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Antimicrobial Ionic Liquid-Based Materials for Biomedical Applications

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Excessive and unwarranted administration of antibiotics has invigorated the evolution of multidrug-resistant microbes. There is, therefore, an urgent need for advanced active compounds. Ionic liquids with short-lived ion-pair structures are highly tunable and have diverse applications. Apart from their unique physicochemical features, the newly discovered biological activities of ionic liquids have fascinated biochemists, microbiologists, and medical scientists. In particular, their antimicrobial properties have opened new vistas in overcoming the current challenges associated with combating antibiotic-resistant pathogens. Discussions regarding ionic liquid derivatives in monomeric and polymeric forms with antimicrobial activities are presented here. The antimicrobial mechanism of ionic liquids and parameters that affect their antimicrobial activities, such as chain length, cation/anion type, cation density, and polymerization, are considered. The potential applications of ionic liquids in the biomedical arena, including regenerative medicine, biosensing, and drug/biomolecule delivery, are presented to stimulate the scientific community to further improve the antimicrobial efficacy of ionic liquids.

1. Introduction

Over the last five decades, the excessive and unwarranted use of antibiotics has invigorated the evolution of multidrug-resistant pathogens on an exponential scale. Such a medical insurgence has been gauged to annihilate the competency of currently available antibiotics, which is becoming a pressing public health concern. Based on a World Health Organization (WHO) report, at least 700 000 people die every year because of antibiotic-resistant bacterial diseases.[1] In 2019 alone, more than 2 868 700 antibiotic-resistant bacterial infections were reported in the USA, and about 35 900 individuals have lost their lives from those infections. Likewise, more than 33 000 Europeans die from

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DOI: 10.1002/adfm.202104148

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antibiotic-resistant bacterial infections per annum. The WHO warns that if no action is taken against antibiotic-resistant bacteria, 10 million people will die every year by 2050. In countries with extreme poverty, antibiotic-resistant bacterial infections may cause as many as 24 million deaths per year.[1] The occurrence of totally antibiotic-resistant tuberculosis in India, Iran, and Italy, for example, is associated with the adaptation of pathogenic bacteria to multiple antibiotics.[2]

Hence, the development of novel antimicrobial materials in the post-antibiotic era is an unrelenting goal for pharmaceutical corporations worldwide.[4] In light of this, ionic liquids, a neoteric class of self-dissociated solvents, are becoming increasingly influential in developing non-antibiotic therapies for combating infectious diseases. The bactericidal properties of ionic liquids can also be tailored by skillful coupling of selected cations and anions, changing the length of the alkyl chain of the cations, or covalent tethering of task-specific functionalities to one or both constituent ions.[4]

The present review provides a synopsis on the antimicrobial activity of ionic liquid-based materials. Detailed parameters that affect the toxicity of these materials are presented. The biological effects and mechanisms of interaction between ionic liquids and bacterial strains as well as mammalian cells are highlighted. The potential applications of ionic liquids in the biomedical arena, including regenerative medicine, drug and biomolecule delivery, and biosensing, will be deliberated to stimulate the scientific community to improve the antimicrobial efficacy of ionic liquids.

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2. Ionic Liquids

Four generations of ionic liquids have been reported based on their molecular structure and physicochemical properties.[3] They may be categorized as follows:

- The first-generation ionic liquids came into the limelight because of their physical properties. The most common first-generation ionic liquids encompass dialkylimidazolium and alkylpyridinium as cations and metal halides as anions. They were recognized as ideal solvents in electrochemical research. Nevertheless, they were sensitive to air and water.[4]
- The second-generation ionic liquids were stable in air and water. Ammonium, alkylpyridinium, dialkylimidazolium, and phosphonium were the common cations, while hexafluorophosphate and tetrafluoroborate were the most commonly employed anions.[5] Second-generation ionic liquids have found a wide range of applications in physical and chemical fields as lubricants, reaction solvents, and energetic materials. However, the toxicity of ionic liquids was not addressed during the first two generations.[5]
- The third-generation ionic liquids included biodegradable and natural ions such as amino acids and choline, or ions with well-known biological activities. This resulted in ionic liquids with targeted and selected biological properties, as the concept of task-specific ionic liquids was introduced during that era.[6] These task-specific ionic liquids were a breakthrough in developing antifungal and antibacterial compounds for biomedical and pharmaceutical applications.[7] They contained covalently linked functionalities which could be tuned for the particular application. Task-specific ionic liquids derived from didecyldimethylammonium bromide and sodium ibuprofen showed both antibacterial and anti-inflammatory properties.[8]
- The fourth-generation ionic liquids were introduced in 2018. These ionic liquids were biocompatible and possessed unique and unpredictable properties in solution or after mixing with other molecular liquids.[4]

2.1. Physicochemical Characteristics

Typically, ionic liquids are molten salts that are liquid at temperatures below 100 °C. They comprise discrete inorganic/organic anions and organic cations (**Figure 1**) with unique physical and chemical properties (**Table 1**).[9–11] Some ionic liquids are liquid at or below room temperature; they are termed as room temperature ionic liquids. Generally speaking, ionic liquids exist in coupling states with a low symmetry structure of organic heterocyclic cations such as imidazolium, tetraalkylammonium, pyrrolidinium, pyridinium, or tetraalkylphosphonium. The counterions consist of inorganic/organic anions such as hexaflurophosphate, tetraflurobromate, octyl sulfate, or nitrate.[12] Ionic liquids are frequently referred to as tunable, tailored, task-specific, or designer solvents because their properties may be tailored by judicious coupling, selection of cations and anions, changing the length of the alkyl chain of the cation, or by covalent tethering of task-specific functionalities to one or both of the constituent ions.[13]

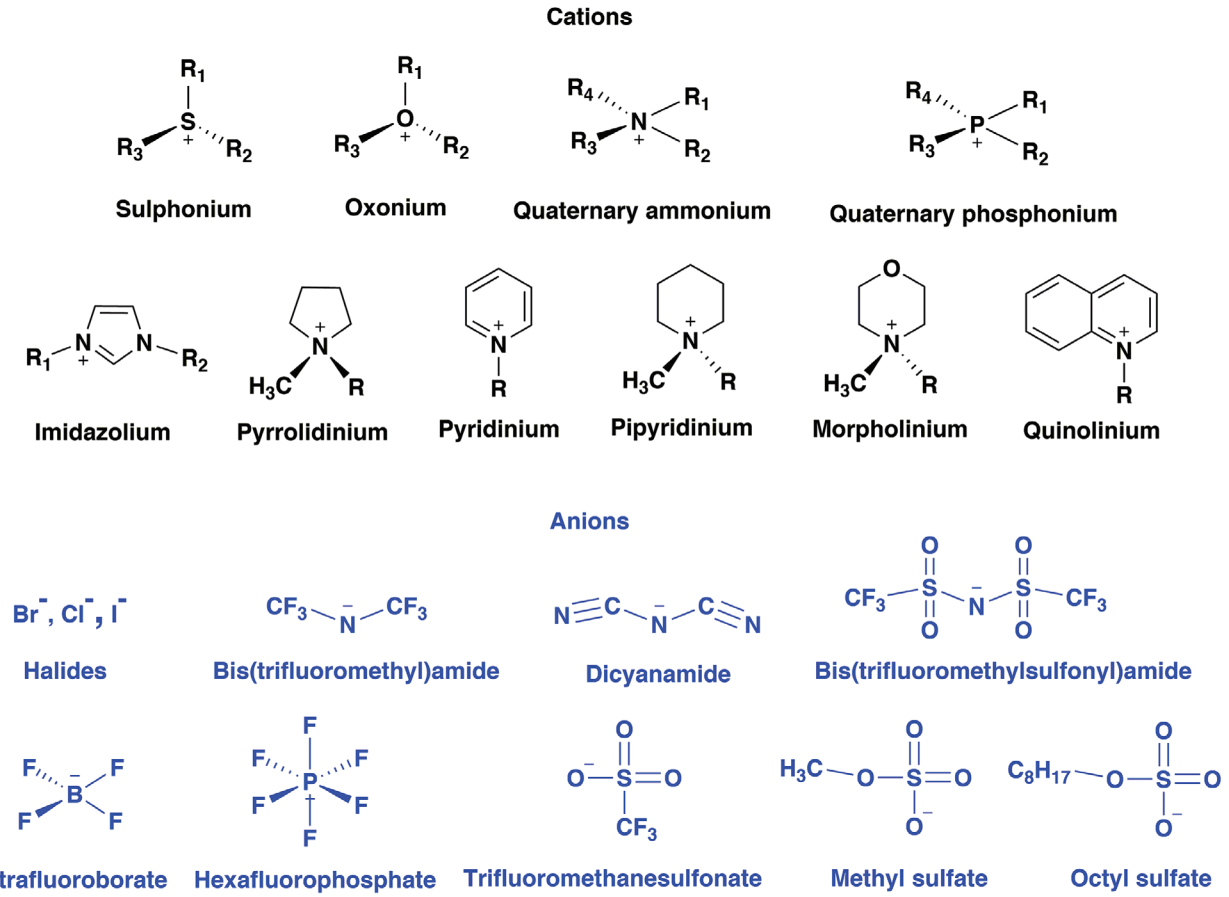

Figure 1. Structures of typical cations and anions commonly used in ionic liquids. Based on the selected types of cation and anion, the compositions of the ionic liquids demonstrate variable physicochemical and biological features.

2.2. Structural Characteristics

The structural characteristics of ionic liquids may be tuned by changing their cation and anion combinations.[14] Functional groups may be covalently tethered to either the anion or cation or both ionic liquid entities. This endows the resulting salt with the capacity to interact with dissolved substrates.[15] However, the introduction of different functionalities renders the synthesis of ionic liquids a long and tedious procedure. Several attempts have been made to synthesize ionic liquids in a facile manner, for example, via one-pot multi-component domino reactions.[16]

In addition, chirality centers can be located in ionic liquid cations and counterions. This enables chiral ionic liquids to be synthesized as enantioselective agents. The chiral ionic liquids may also be used in anion-directed chirality transfer

Table 1. Physical and chemical properties of ionic liquids.

Conductivity	Better ionic conductivity than organic solvents and electrolytes due to the presence of a large number of mobile ions per unit volume.[9]
	High thermal conductivity and heat capacity.
Density	Higher than water.[9]
Electrochemical	A very wide electrochemical window in which the electrolyte is either reduced or oxidized at an electrode [9]
Melting point	Less than 100 °C
Polarity	Highly polar
Solubility	Both miscible (1-butyl-3-methylimidazolium tetrafluoroborate) and immiscible (1-decyl-3-methylimidazolium bis(trifluoromethylsulfonyl) imide) in water. The miscibility depends on the structure and physicochemical properties of the anion and cation present.[10]
Stability	Chemically and thermally very stable. Some ionic liquids are stable up to 450 °C,[10] while most ionic liquids are stable toward organic and inorganic compounds.[11]
Vapor pressure	Vapor pressure is very low because of strong ionic interactions.[12]
Viscosity	Comparatively more viscous than common molecular solvents.[9]

reactions.[17] Because of their chiral nature, the synthesis of chiral ionic liquids is a challenging and multi-step procedure.[18]

Switchable polarity ionic liquids can change their physical properties through the addition or removal of molecular triggers.[19] Proton transfer reaction was used to synthesize moisture sensitive, low polarity, switchable polarity ionic liquids from amidine/fluoroalcohol and guanidine/fluoroalcohol. These low polarity entities were converted to high polarity switchable polarity ionic liquids upon treatment with carbon dioxide under mild conditions.[19]

Bio-ionic liquids are ecologically safe and biocompatible, with an extensive range of applications. Biological ionic liquids (bio-ionic liquids) have been synthesized through green channels to address the toxicity and biodegradability issues using amino acids, glucose, and carboxylic acids. These ecologically safe materials have been synthesized, for instance, by the reaction between cholinium cation and amino acid anions (aspartic acid, glutamic acid, and histidine).[20] Bio-ionic liquids demonstrate excellent anti-wear, friction reduction properties, as well as biodegradability. Among the bio-ionic liquids, (2-hydroxyethyl)-ammonium lactate ionic liquids are 95% biodegradable based on European standards.[21] As another example, an oral insulin formulation developed from a choline-based ionic liquid is highly effective as oral delivery vehicles.[22]

The introduction of energetic functional groups into the cation of ionic liquids (e.g., *N*-rich ammonium, hydrazinium, tetrazolium, *N*-heteroaromatic rings) and the use of various anions (e.g., nitro- and cyano-containing borohydride based anions) result in energetic ionic liquids with aerospace, military, and mining industries applications. The energetic behavior of these materials is attributed to a reaction with an external oxidizer. Some of these materials are very sensitive to ambient oxidative conditions.[23]

Stoichiometric neutralization of certain Brønsted acids and Brønsted bases is used to synthesize protic ionic liquids. Because of mobile protons, protic ionic liquids exhibit rapid proton conduction and facile hydrogen oxidation and oxygen reduction reactions.[23] High fluidity and ionicity make protic ionic liquids highly conductive. The combination of properties such as relatively low vapor pressure, high ionicity, and proton exchange kinetics renders protic ionic liquids excellent electrolytes for fuel cell applications. And, aprotic ionic liquids are synthesized through the Menshutkin reaction, in which the mobile proton (present in protic ionic liquid) is replaced by an alkyl group. Toxicity evaluation of aquatic organisms shows that aprotic ionic liquids are comparatively less toxic and more biodegradable than protic ionic liquids.[24]

Metallic ionic liquids, also referred to as liquid metal catalysts are synthesized by a reaction between transition or main group metal salts and an ionic liquid.[25] They have a wide range of catalytic applications. Basic ionic liquids are used as eco-friendly solvents and catalysts. They are noncorrosive, nonvolatile, and immiscible in many organic solvents. Because of their robust activity and selectivity, basic ionic liquids are excellent alternates to conventional inorganic bases such as KOH, NaOH, or $NaHCO_3$.[26]

3. Antimicrobial Mechanism

Ionic liquids can cross bacterial membranes, enter the cytosol and alter the membrane characteristics of the bacterial cell wall. These characteristics include membrane potential, fluidity, viscoelasticity, and the arrangement of phospholipids. Alteration of the cell membrane fluidity changes the diffusion rate and stability of the proteins within the membrane, with severe impacts on membrane function such as molecule transportation, recognition, migration, adhesion, and mechanotransduction.[27–29] Ionic liquids also alter membrane permeability by creating pores that result in irreversible damage.[30,31]

The antibacterial properties of ionic liquids are attributed to: I) Adsorption: ionic liquid are attracted to the cell membranes. II) Electrostatic interaction: the deactivation of membrane proteins and interaction of the ionic liquid with membrane phospholipids. III) Penetration: disorganization and disintegration of the phospholipid bilayer and leakage of intracellular cytoplasm. IV) Cell wall destruction: cell lysis.[32,33] The overall scheme of cell wall destruction in Gram-negative and Gram-positive bacteria via penetration of ionic liquids, as well as the interaction kinetics of ionic liquids with the bacterial cell wall/membrane, are depicted in **Figure 2**. These phenomena are attributed to the perturbation of biochemical gradients between the cytoplasm and the outer environment after exposure to ionic liquids resulting in penetration of extracellular materials into the cytoplasm, or diffusion of intracellular contents out of the cell.[5] In addition, ionic liquids may interact with transmembrane proteins that alter their capability to transport lipids, water, and nutrients.[34–36]

Gram-positive and Gram-negative bacteria share the common feature of carrying negative charges on their surfaces. Gram-negative bacteria's cell wall contains lipopolysaccharides linked to the outer membrane phospholipid bilayer wherein zwitterionic compounds are attached.[37–40] The cell wall of Gram-positive bacteria contains teichoic acids, which are copolymers of glycerol phosphate/ribitol phosphate and carbohydrates linked via phosphodiester bonds (**Figure 3**A,B).[41,42] Ionic liquids have been formulated with different aliphatic chain lengths to tune their interactions with the cell membrane of Gram-positive bacteria. In Figure 3C, the different distances between ionic liquids and the cell membrane were simulated by choosing two different *N*-cinnamylmidazolium salts. 1-decyl-3-cinnamylimidazolium chloride ([CDIM][Cl]) that contains a higher number of methyl groups was incorporated into the phospholipid bilayer and remained within the membrane for the entire simulation period. The scenario represents an example of passive diffusion through the membrane. Conversely, 1-methyl-3-cinnamylimidazolium chloride ([CMIM][Cl]) was not incorporated into the phospholipid bilayer due to the lack of hydrophobicity. Simulation of the penetration of [CDIM][Cl] into the membrane by molecular dynamic methods revealed that the imidazole polar ring interacted with the aliphatic groups of the lipid alkyl chains (Figure 3D).[41]

4. Cytotoxicity

Apart from antimicrobial activity, mammalian cell cytotoxicity is also an essential criterion for developing antimicrobial platforms. The application of microbicidal agents (e.g., cationic compounds such as ionic liquids) in the biomedical arena is seriously limited by their cytotoxicity.[43,44] Cell toxicity of the earlier generations of ionic liquids is well recognized, severely restricting their biomedical applications. However, researchers

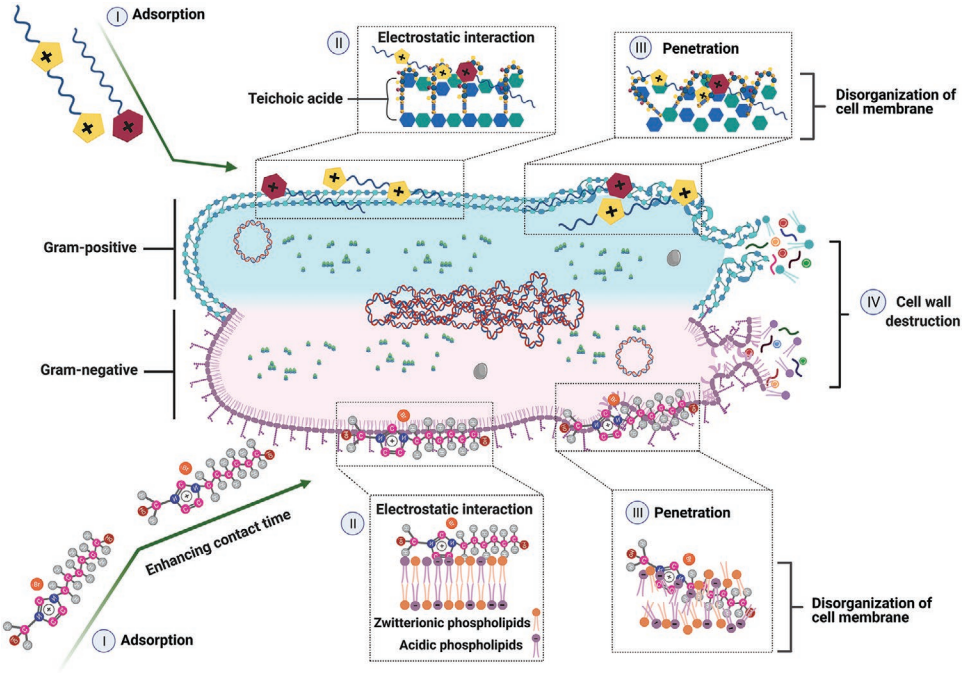

Figure 2. Mechanism of cell wall destruction from Gram-negative bacteria and Gram-positive bacteria by ionic liquids. Bacterial cell death is attributed to four different stages, including I) adsorption: the kinetics of ionic liquids approaching the bacterial cell wall/membrane; II) electrostatic interaction: interaction between the zwitterionic phospholipid bilayer functional groups and ionic liquids, III) penetration: penetration of ionic liquid and, consequently, disorganization of cell membrane, and IV) cell wall destruction: cell lysis.

have taken advantage of these adverse effects of ionic liquids to utilize them as antibacterial agents for infection control. Scientists have undertaken significant efforts to identify the potential association between the structural features of ionic liquids and their cytotoxicity. It has been reported that dicationic ionic liquids generally induce less cytotoxicity compared to the monocationic counterparts. Increasing the lipophilicity of monocationic ionic liquids by elongation of their alkyl chains results in higher cytotoxicity. As the alkyl chain is "trapped" between both cationic moieties, the impact of the length of the linkage alkyl chain of dicationic ionic liquids on cytotoxicity has not yet been revealed.[45] Cytotoxicity of ionic liquids not only depends on their structure, but is also related to the specific cell type. Bacterial membranes are predominantly composed of anionic lipids, whereas mammalian cells are largely composed of zwitterionic lipids that are neutral at physiologic pH. This difference in the electrostatic charges of the membranes causes targeted tropism of the antimicrobial agents to the negatively charged bacteria. In addition, the presence of cholesterol in the mammalian cell membrane protects and reduces cytotoxicity after exposure of these cells to microbiocidal components.[46,47] Nevertheless, depending on the concentration and structures of ionic liquids, cytotoxicity may still occur in mammalian cells.

Cytotoxicity of ionic liquids usually results in the impairment of the mammalian cell membrane. This is associated with the lipophilicity of alkyl chains and anions of ionic liquids (**Figure 4**). The insertion of ionic chains alters the cell's swelling status and ultimately causes disintegration of the lipid bilayer. The intensity of cytotoxicity correlates positively with the length of the alkyl chain. The longer alkyl chain, the stronger, the ionic liquid–lipid bilayer interactions, and the more severe the ionic liquid–lipid bilayer interactions, and the more severe the disruption of the mammalian cell membrane.[48] Moreover, the effect of the headgroup on the severity of cytotoxicity is primarily related to the lipophilicity of the ionic liquid.[49]

X-ray scattering, light, and fluorescence imaging have been used to provide evidence that ionic liquids interrupt the lipid bilayer of the mammalian cell membrane by end-capping the hydrophobic edge of the lipid bilayer (Figure 4A,B).[50] Different mechanisms are involved in ionic liquid cytotoxicity. For example, the insertion of cationic agents into the cell membrane causes mitochondrial dysfunction. Ionic liquids can also penetrate into the mitochondria and cause damage to the generation of adenosine triphosphate (ATP).[48] The latter is involved in many signaling pathways associated with cell growth, differentiation, and death via apoptosis or necrosis, according to the type of ionic liquids and cell type.[51] Ionic liquids can collapse the mitochondrial membrane potential, which induces apoptosis by releasing cytochrome C into the cytosol. Interaction of ionic liquids with the mitochondria also results in reactive oxygen species (ROS) production that can destroy many biological macromolecules such as membrane lipids, deoxyribonucleic acids, and enzymes (Figure 4C). The ionic liquids interact directly with ATP because of the highly charged status of ATP. These interactions result in the conversion of ATP to adenosine diphosphate (ADP).[51]

Treatment of PC12 cell line with 1-octyl-3-methylimidazolium chloride increased intracellular Ca^{2+} and ROS production. This, in turn, resulted in the exhaustion of cellular ATP and mitochondrial permeability transition.[50] Bending instabilities through the insertion of ionic liquids into the mammalian cell membrane initiates morphological reorganization of the cell membrane and alters cellular function.[48]

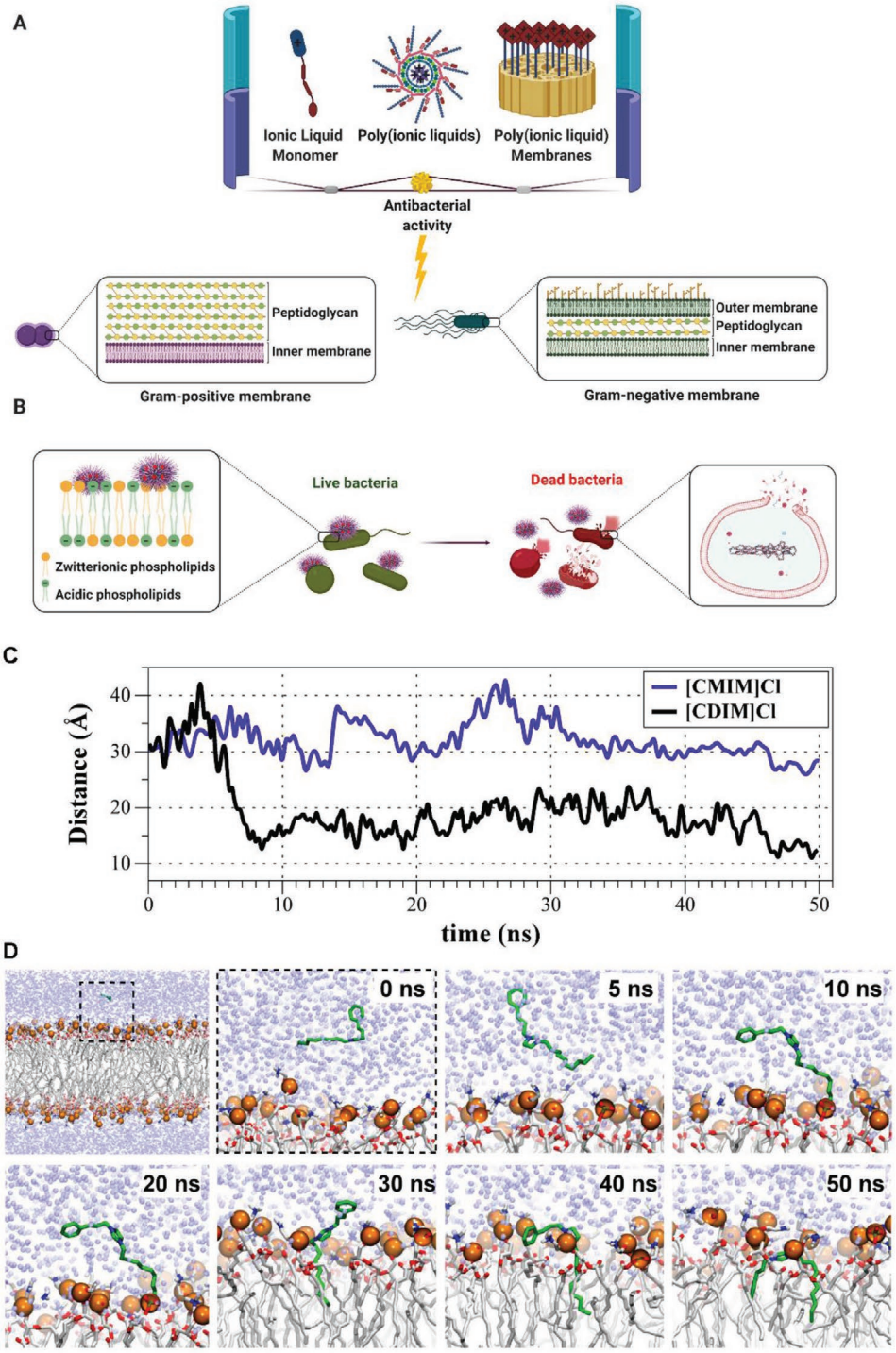

Figure 3. Bacterial cell interaction with ionic liquids. A) Ionic liquids interact with cell membranes of Gram-positive and Gram-negative bacteria, causing cell death through electrostatic interactions between cationic moieties of the ionic liquids and phosphate groups of the microbial cell. B) Bilayer chemical structures of bacteria (Gram-positive and Gram-negative) and their interactions with membrane functions. C) Simulation time based on distances between the ionic liquids [CDIM][Cl] (black) and [CMIM][Cl] (blue) D) Molecular dynamics simulations of the [CDIM][Cl] penetration into the bacteria cell membrane for 50 ns. [CDIM][Cl]: 1-decyl-3-cinnamylimidazolium chloride. [CMIM][Cl]: 1-methyl-3-cinnamylimidazolium chloride. C,D) Reproduced under the terms of the CC-BY license.[41] Copyright 2018, MDPI.

The physicochemical properties of ionic liquids depend on three parameters, alkyl chain length, the nature or type of organic cation, and inorganic anion.[52] Any alteration in the aforementioned parameters can alter the antimicrobial activity of ionic liquids. The parameters that affect toxicity against bacterial and mammalian cells are discussed in the following subsections.

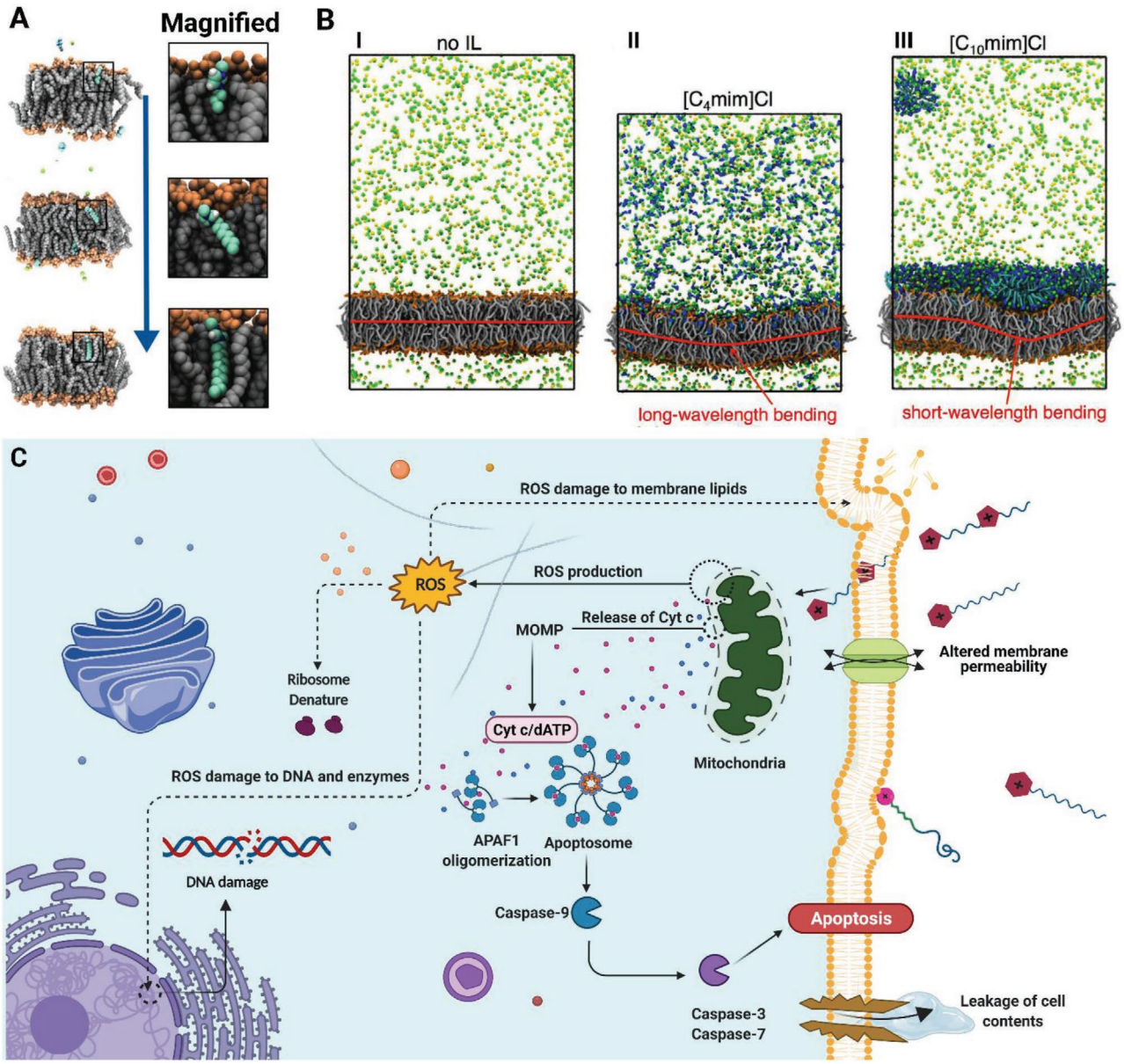

Figure 4. Impact of ionic liquid on the mammalian cell. A) Atomistic simulations of 1-palmitoyl-2-oleoyl-phosphatidylcholine (POPC) bilayer system with $[C_4mim]Cl$, $[C_8mim]Cl$, and $[C_{12}mim]Cl$ demonstrated spontaneous insertion of the imidazolium cations into the lipid bilayer. The concentrations of ionic liquids ranged from $5–50 \times 10^{-3}$ M. B) I–III) Snapshots of the coarse-grained simulations of a POPC bilayer system I) without an ionic liquid II) with $[C_4mim]Cl$, and III) with $[C_{10}mim]Cl$ (top row). Ionic liquid and NaCl (sodium-yellow; chloride-green) buffer concentrations are $\approx 200 \times 10^{-3}$ and $\approx 160 \times 10^{-3}$ M, respectively. In (III), an almost fully covered monolayer of adsorbed $[C_{10}mim]Cl$ is formed at the lipid bilayer aqueous interface. Reproduced under the terms of the CC-BY license.[48] Copyright 2016, Springer Nature. C) Schematic illustration of the possible effects and signaling pathway for the interaction of an ionic liquid with the mammalian cell membrane. After penetrating the cell membrane, further interaction of the ionic liquid with the mitochondrial outer membrane causes collapse of the mitochondrial membrane potential (MOMP), the release of cytochrome C into the cytosol, activation of caspase 3/7 apoptosis pathway, as well as production of ROS. These phenomena result in damage of membrane lipids, DNA, and enzymes.

5. Parameters that Control Antimicrobial Activity

5.1. Effect of Alkyl Chain Length of Ionic Liquids

The length of the substitute alkyl chain is an important factor that affects the antibacterial properties of ionic liquids. The antibacterial efficacy of ionic liquids generally increases with increasing alkyl chain lengths, until a threshold value (critical point) is reached; further increase in chain length causes a decline in antibacterial activity.[53] Increasing the hydrophobicity of an alkyl chain or lack of polar functional groups (such as hydroxyl and ether groups) in the ionic liquid improves antibacterial efficacy.[54] Ionic liquids with longer carbon chains (more than ten carbon atoms) demonstrate more potent antimicrobial activity. Long alkyl chains destabilize the bacteria cell membrane, enabling the alkyl chain to penetrate the

phospholipid bilayer. This, in turn, induces structural damage to the bacterial cell membrane.[5] The antibacterial activities of imidazolium-based ionic liquids were tested using *Escherichia coli* and *Staphylococcus aureus* as model microorganisms. It was found that increasing the alkyl chain length intensified the van der Waals interactions, leading to lower minimal inhibitory concentration (MIC) values.[5,41,55] The MIC values were associated with alkyl chain length substitution at the N3 position of the imidazolium cations. Longer alkyl chains were responsible for the lower MIC values of ionic liquid monomers.[56,57] The threshold value (i.e., the best chain length) for a specific ionic liquid depends on its structure and the final platform (i.e., hydrophobicity, crosslinking density of the final fabricated polymer and composite).[53]

The hydrophobic alkyl chain portion of the ionic liquid penetrates the bacterial cell membrane, causes membrane disruption, and ultimately cell death. Antibacterial efficacy is also correlated with the hydrophobic nature of an ionic liquid. In one study, 1-alkyl-4-hydroxy-1-methylpiperidinium cations with alkyl chain lengths ranging from 2 to 16 carbons and mandelate anion were investigated. Cations with a longer alkyl chain (longer than octyl) possessed considerable antimicrobial activity against pathogenic microorganisms, enabling them to function as potent disinfectants.[58,59]

Another factor that influences the interaction between an ionic liquid and the membrane lipid bilayer is molecular size. The latter is a function of chain length. To investigate this issue, a series of flexible diketopyrrolopyrrole-based ionic liquids with various chain lengths were prepared (**Figure 5**).[60] These ionic liquids had chain lengths that varied from 3 to 12 alkyls (designated as IL-3 to IL-12) and possessed molecular sizes ranging from 1.95 to 4.2 nm. The ionic liquid IL-6 was found to effectively disrupt cell membranes due to bilayer thinning. Ionic liquid derivatives with the longest molecular length (i.e., IL-10 and IL-12) created more disorder within the membrane bilayer, resulting in membrane disruption (Figure 5A,B). The lipid chain and membrane order and structural integrity were investigated using simulation of the deuterium order parameter. Generally speaking, a higher value of deuterium order parameters reflects a more ordered phospholipid arrangement or less membrane perturbation. In that simulation study, the ionic liquid with the shortest chain length (i.e., IL-3) only resided on one side of the phospholipid bilayer. The IL-3 induced the lowest destructive effect and the least potent antibacterial activity. In contrast, long-chain ionic liquids created the most severe disturbance of the phospholipid bilayer of bacterial cell membranes (Figure 5A,B).[60] The experimental data were consistent with the molecular dynamics simulation results. Low MIC values were found for IL-6, IL-10, and IL-12 (Figure 5C). The biocompatibility of the ionic liquids was evaluated by examining their hemolytic activity and cytotoxicity. Hemolysis activity of the ionic liquids was more pronounced with increased alkyl chain length. This was attributed to the increase in hydrophobicity associated with the longer aliphatic chains. Cytotoxicity evaluation using eukaryotic L929 and RAW 264.7 cells indicated that cytotoxicity was dose-dependent. Although ionic liquids had acceptable biocompatibility at a concentration of 32×10^{-6} M, they were cytotoxic beyond this concentration.[60]

Surface active ionic liquids possessing amphiphilic structures can undergo spontaneous self-assembly. Depending on the structure and hydrophilic–hydrophobic balance, they can self-assemble into spherical micelles, disks, rods, planar bilayers, vesicles, threads, networks, tubes, as well as twisted and helical ribbons.[61] Self-assembled ionic liquids attracted attention because of their potent antibacterial property. These self-assembled entities possess better antimicrobial activity than the corresponding monomers because of the micelles' higher surfactant concentrations or cationic charge concentrations. This results in strong interactions with bacteria cell membranes and, in turn, cell lysis.[62] An important parameter that affects the antimicrobial activity of self-assemble ionic liquids is their alky chain length. When alkyl chains are covalently linked to a single head group, hydrophobicity is enhanced with an increase in the alkyl chain length.[63] A cut-off phenomenon was observed with respect to the effect of alkyl chain length on the antibacterial activities of *N,N*-dimethylalkylamine *N*-oxides. The maximum antimicrobial activity against *S. aureus* and *E. coli* was found for specimens with hexadecyl (C_{16}) or tetradecyl (C_{14}) chains.[63] The free volume mechanism may explain this phenomenon. When surfactant molecules are inserting into the bacteria membrane, they can create a free volume underneath their hydrophobic alkyl chain due to their asymmetric conical structure. The membrane permeability that resulted from the created free volume affects bacteria viability. Short alkyl chains create a large free volume due to their larger conical asymmetry structure. However, they have weak interactions with membrane lipids because of their small membrane partition coefficients. Longer alkyl chains have higher partition coefficients and lower created free volumes because of decreased conical asymmetry structure of the cationic surfactant molecules. Consequently, the cationic surfactants with medium alkyl chains have sufficient membrane partition coefficient to be inserted into the bacterial membrane to produce the maximal total free volume, maximal membrane permeability, and higher bacteria killing rate.[44,63] Double-tailed or gemini cationic surfactants such as di-*N*-dodecyldimethylammonium halide with an alkyl spacer range of 2C–12C demonstrated more potent antimicrobial activities against *S. aureus* and *E. coli* at spacer lengths between 5C and 8C; antimicrobial activity decreases when the spacer length is longer than 8C.[44,63]

5.2. Effect of Cations and Anions

The cationic and anionic composition of an ionic liquid also affects its antibacterial activity.[64] Active pharmaceutical ingredients and cationic surfactants interact with the negative charges present on the bacterial cell membranes and cause membrane disruption.[65]

Ionic liquids with pyrithione, pyridinium, imidazolium, and guanidinium cations possess inhibitory effects against pathogenic/nonpathogenic bacteria/fungi.[66–68] For ionic liquids containing ammonium, pyrrolidinium, imidazolium, pyridinium, piperidinium, morpholinium, or cholinium cations the same anion (lauroyl sarcosinate), the one that contains the pyridinium cation had the strongest antibacterial activities against Gram-positive and Gram-negative bacteria. The rest of

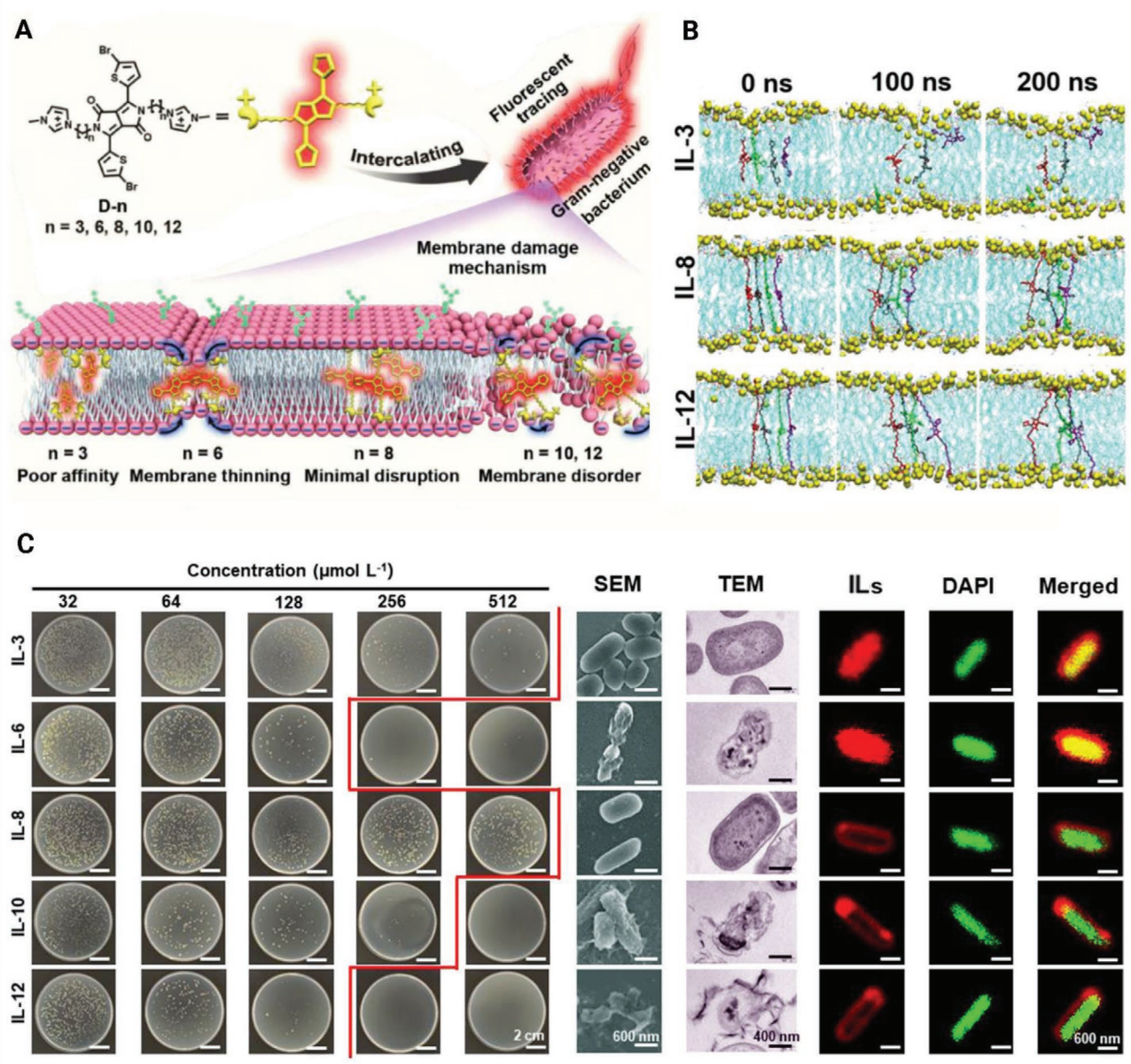

Figure 5. Effect of alkyl chain length on antibacterial activity of ionic liquids. A) Schematic of membrane damage by a series of flexible fluorescent diketopyrrolopyrrole-based ionic liquid derivatives (ILs) with different alkyl chain lengths (molecular size ranging from 1.95 to 4.2 nm) against Gram-negative bacteria. B) Sequential snapshots of simulations of interactions between ILs and the phospholipid bilayer. C) Scanning electron microscopy, transmission electron microscopy, and confocal laser scanning microscopy (CLSM) images of bacteria colonies incubated with different ionic liquids for 12 h. The red fluorescence identified in the live-dead stained *Pseudomonas aeruginosa* after treatment with 64 μmol L^{-1} of ionic liquid for 4 h was indicative of dead bacteria. The CLSM results showed that the ILs penetrated bacteria through their cell membrane. Reproduced with permission.[60] Copyright 2020, American Chemical Society.

the cations demonstrated moderate to low activity against the tested bacteria. This phenomenon may be related to the impact of aromaticity of the cations on antibacterial activity. In addition, due to the weak ion-pairing of pyridinium cation in comparison with imidazolium cation, pyridinium cations are more effective as antibacterial agents.[69]

Anions of ionic liquids also possess antibacterial activities and have demonstrated impressive inhibitory effects against biofilm-forming microorganisms. Their effects are secondary to those of the cations. Because of the limited types of anions reported, no consistent conclusions may be deduced regarding their potency. In one study,[70] the antibacterial activities of ionic liquids containing three separate anions (Br^-, BF_4^- and PF_6^-) were investigated. Ionic liquids containing Br^- possess stronger antibacterial activity against *E. coli* than BF_4^- and PF_6^-. Examination of the water contact angles of ionic liquids containing the different anions indicated that Br^- is less hydrophobic than BF_4^- and PF_6^-. The antibacterial effect of anions appears to be affected by their dissociation constant and hydrophobicity. The hydrophobic anions BF_4^- and PF_6^- (unlike Br^-), have poor

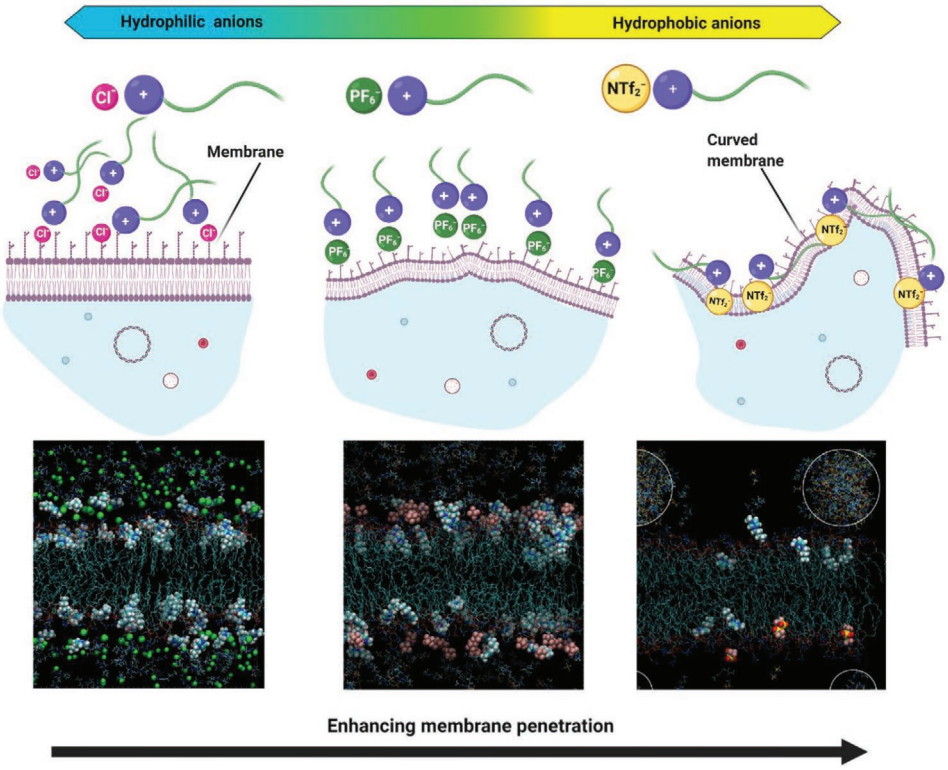

Figure 6. The effect of anion-induced hydrophobicity on the antibacterial activity of ionic liquids. The interaction mechanism includes I) Small hydrophilic anions that remain on the external surface of the membrane. II) Formation of a thin layer of PF_6^- anions at the boundary due to the interaction between the anions and the phospholipid heads of the membrane. III) The more hydrophobic anions such as bis(tri-fluoromethylsulfonyl)imide (NTf_2^-) penetrate the membrane and insert the hydrocarbon tail into the membrane. The simulation images: Reproduced with permission.[74] Copyright 2012, American Chemical Society.

solvation and dissociation, which prevent the long alkyl chain of imidazolium from penetrating the bacterial membrane.[71,72]

Micellization of surface-active ionic liquids is affected by the basicity of their counterions as well as the interaction between cations and counterions. When the basicity of the counterion increases, the interaction between the head group and the counterion becomes stronger. This results in more effective circumvention of the electrostatic repulsion among the head groups, which in turn, leads to a low critical micellization concentration (CMC) and a tight molecular packing. When Br^- is replaced by BF_4^-, the greater likelihood of interaction between the aromatic hydrogen atoms, primarily H_2, and BF_4^- leads to more intimate interaction between cations and counterions. Consequently, this interaction results in a more effective screening of the electrostatic repulsion among the cations, enabling tighter molecular packing at the air-liquid interface and reducing the CMC.[73]

Anions are involved in simultaneous interaction between water molecules and the phospholipid bilayer. Small hydrophilic anions such as Cl^- cannot pass through the cell membrane, while more hydrophobic anions such as PF_6^- formed a thin layer at the lipid-water interface. Coulombic attraction between the cations in the bilayer and anions may stabilize the anion film. Interaction of PF_6^- with the polar phospholipid head further reinforces this stabilization. Hydrophobic anions such as bis(trifluoromethylsulfonyl)imide (NTf_2^-) may be incorporated into the hydrocarbon tails of the membrane lipid bilayer to disturb the phospholipid arrangements, with the cations located outside the membrane (**Figure 6**). Apart from the anionic effect, the aromaticity and size of cations also affect ionic liquids' water solubility or cavitation potential.[74]

5.3. Effect of Cation Number Density

Cations present in ionic liquids can interact with the outer membrane (phosphate groups of Gram-negative bacteria and teichoic acid groups of Gram-positive bacteria) through electrostatic attraction.[37,38,75] Increase in the cation number density (i.e., number of cations per ionic liquid structure results in stronger electrostatic interaction between cations and the outer membrane. The augmented adsorption of ionic liquid molecules on the bacteria membrane results in more rapid and efficient bacteria eradication.[29,76] The antibacterial activities of imidazolium-based ionic liquids with different cation number densities (viz. mono- or bis-cations) were evaluated against *E. coli* and *S. aureus*.[31] In many instances, bisimidazolium systems possess more potent antibacterial properties and lower MIC values than the corresponding mono-imidazolium analogs (**Figure 7**). However, there are exceptions to this trend, with the mono-imidazolium compounds possessing more potent antibacterial properties than bisimidazolium

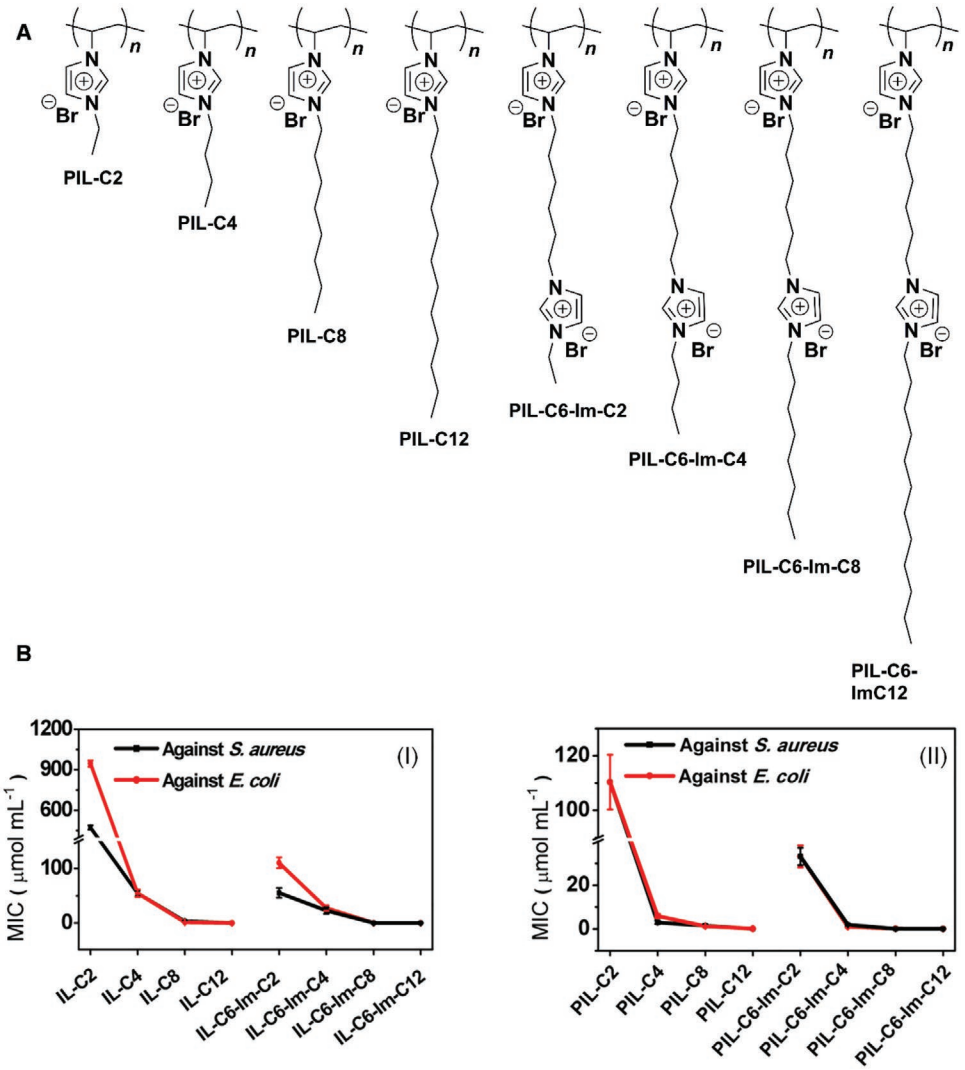

Figure 7. Effect of polymerization of ionic liquids on antibacterial activity. A) Chemical structure of imidazolium-based ionic liquid homopolymers. B) Minimum Inhibitory Concentration (MIC) values against *S. aureus* and *E. coli* in solutions of ionic liquid vinylic monomers I) and their corresponding polymerized ionic liquids II). The longer alkyl chain and higher charge density result in lower MICs and more potent antibacterial activities of both the ionic liquid monomers and the polymerized ionic liquids in bacteria suspension. In addition, polymerized ionic liquids demonstrated relatively lower MIC values in comparison with the corresponding ionic liquid monomers. That is, the polymerized ionic liquids have more potent antimicrobial activities than ionic liquid monomers. Reproduced with permission.[31] Copyright 2016, American Chemical Society.

compounds.[77] Although bis-cations have been reported to be more effective than the related mono-cation, other factors may affect and improve the antibacterial potency of the mono-cations.

The number of cations and hydrophobicity are important parameters that affect their antimicrobial activities of self-assembled ionic liquids. The antibacterial activity of surfactants may be enhanced by increasing the number of cationic head groups. Dimeric surfactants with two cationic head groups and two hydrophobic chains demonstrated more potent antibacterial activity than the corresponding monomeric counterparts.[78] Oligomeric surfactants, consisting of three or more amphiphilic units attached by spacer groups, possessed excellent antibacterial activity.[79,80] Recent studies reported that the antibacterial activity and biocompatibility of surfactants might be improved by including amide linkages.[44,81] The antibacterial activities of three cationic ammonium-based surfactants (viz. a trimeric surfactant (DTAD),[79] a tetrameric surfactant (PATC),[82] and a hexameric surfactant (PAHB)[80]) were investigated (**Figure 8**A). These ionic liquids were capable of self-assembling into cationic micelles and exhibited antibacterial activity against *E. coli* (Figure 8B). As the numbers of cationic headgroup increases, their antibacterial efficacy was in the order: PAHB > PATC > DTAD. By using scamming electron microscopy examination and colony-forming units (CFU) counting of *E. coli* before and after exposure to the ionic liquid surfactants, it was found that the cationic micelles could interact with the negatively charged cell membrane of *E. coli*. The interaction resulted in bacteria cell membrane rupture, leakage of cytoplasm, and cell death (Figure 8C,D). Cytotoxicity evaluation further indicated that these surfactants possessed minimal toxicity on the immortal human HeLa cell line.[62]

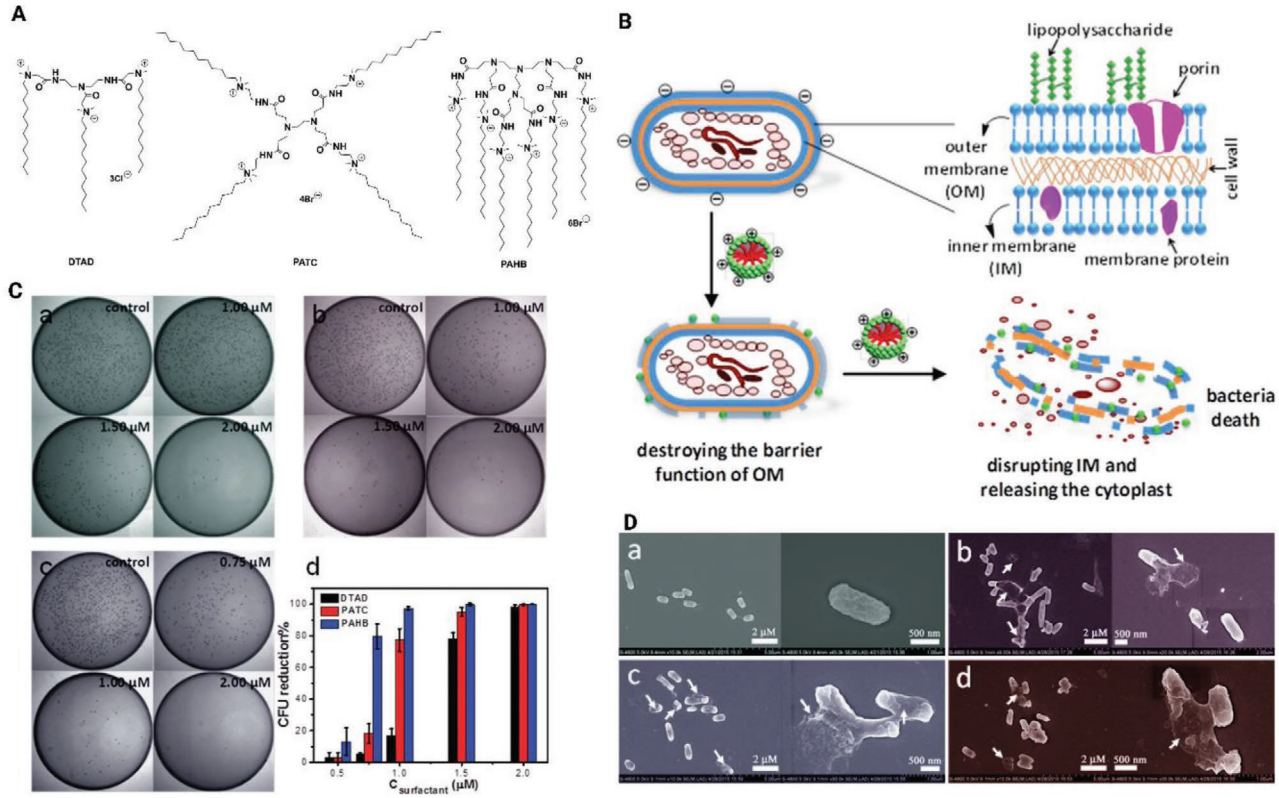

Figure 8. Antibacterial activity of micellized cationic surfactants. A) Chemical structures of surfactants based on cationic ammonium: trimeric surfactant (DTAD), tetrameric surfactant (PATC), and hexameric surfactant (PAHB). B) Schematic of the purported antibacterial mechanism of the cationic surfactant micelles (caused by self-assembly of the cationic surfactant) to *E. coli*. C) Number of colony forming units (CFU) of *E. coli* after addition of surfactants with different concentrations on agar culture plates: a) DTAD, b) PATC, c) PAHB, and d) antibacterial activity of DTAD, PATC and PAHB against *E. coli*. D) Scanning electron microscopy images of *E. coli* before a) and after b–d) incubation with the micelles created from b) DTAD, c) PATC, and d) PAHB at a concentration of 2.0×10^{-6} M. Bacteria with collapsed membranes (indicative of dead bacteria) are depicted by arrows. Reproduced with permission.[62] Copyright 2016, American Chemical Society.

5.4. Effect of Polymerization: Monomers versus Polymers

Most of the unique features of ionic liquids can be integrated into polymerized ionic liquids by polymerization of the corresponding ionic liquid monomers. Polymerized ionic liquids may be designed by adjusting their charge number density, molecular weight, and hydrophobicity to achieve more potent antibacterial efficacy and lower cytotoxicity.[83–88] The antibacterial activities of imidazolium-based ionic liquid monomers and their corresponding homopolymers were examined against Gram-positive *S. aureus* and Gram-negative *E. coli* as model microorganisms (Figure 7). Polymerized ionic liquids had lower MIC values than the corresponding ionic liquid monomers.[31] The polymerized ionic liquids contain many cationic sites (imidazolium) along their chains. When a segment of the polymerized ionic liquid random coil electrostatically interacts with the bacteria cell wall or membrane, the rest of random coil can rearrange and spread over the membrane. Hence, infiltration of the alkyl chains derived from ionic liquids occurs over a large area on the bacteria cell surface simultaneously. This helps to destroy bacteria more efficiently. Hemolysis rate analysis and cytotoxicity assay were used to confirm the nontoxicity of polymerized ionic liquids on red blood cells and human dermal fibroblasts.

In another study, the antibacterial activities of pyrrolidinium-based ionic liquid monomers and their corresponding homopolymers were investigated (**Figure 9**A,B). Growth curves of *S. aureus* and *E. coli* incubated with the pyrrolidinium-based ionic liquid monomers I, II) and the corresponding homopolymers III, IV) are shown in Figure 9C. Both the pyrrolidinium-based ionic liquid monomers and their homopolymers effectively killed the bacteria and inhibited their growth. The polymerized ionic liquids had relatively lower MIC values than the monomeric ionic liquids, with the forming exhibiting better antimicrobial activities.[29] The antibacterial effect of *N*-substitutions of pyrrolidinium cations in both the monomers and homopolymers was also investigated. The results indicated that the MIC values decreased with alkyl chain length. Entities with longer alkyl chains exhibited more potent antibacterial activities. Cytotoxicity assay of pyrrolidinium-based ionic liquids toward fibroblasts indicated that they were biocompatible. The relative growth rate of fibroblasts was higher than 90%.[29]

6. Biomedical Applications

6.1. Regenerative Medicine

Tissue engineering is an interdisciplinary field of science that develops strategies to repair and/or regenerate injured or damaged tissues of the body.[89–91] Tissue healing or regeneration

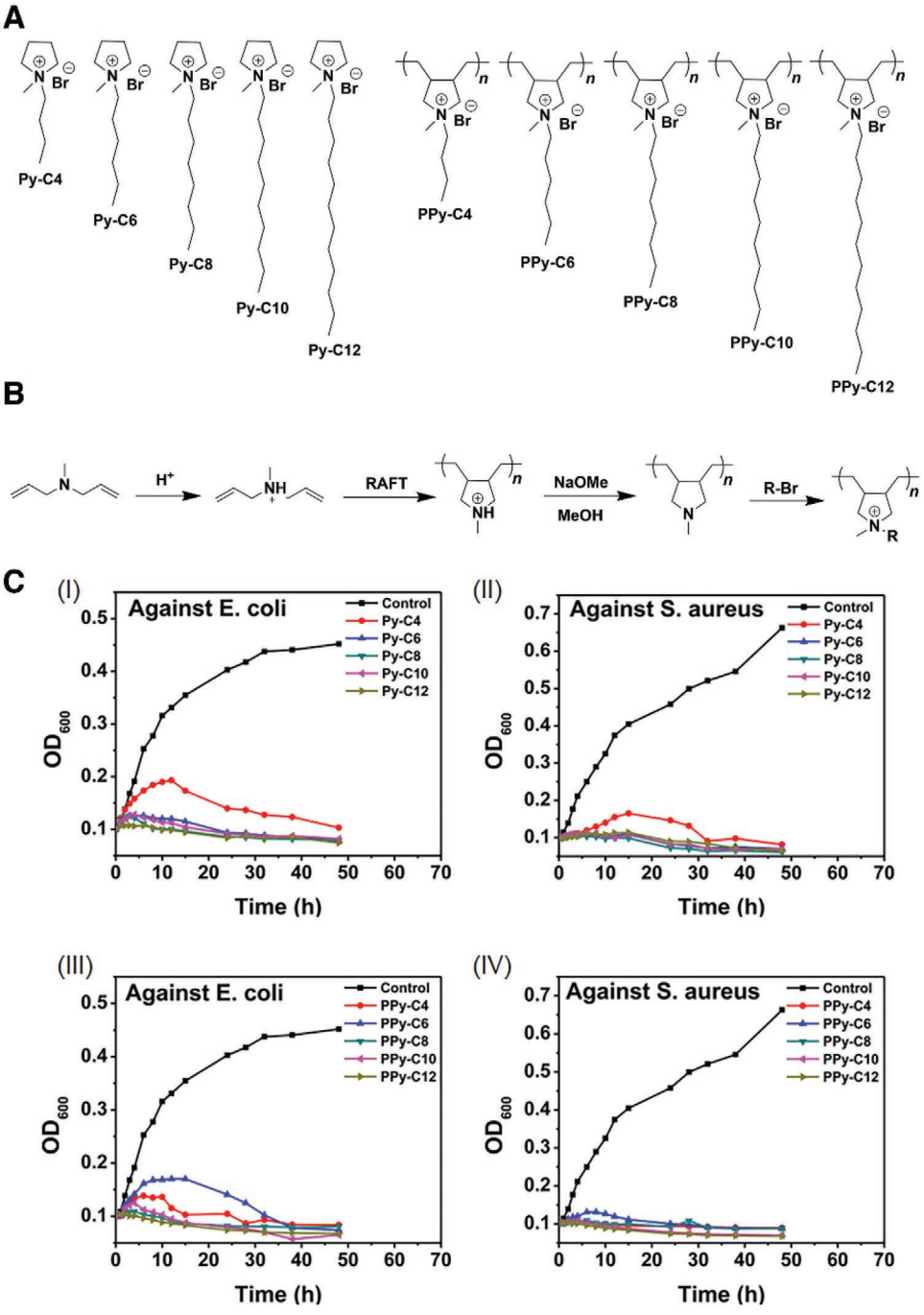

Figure 9. Effect of polymerization of ionic liquids on antibacterial activity. A) Chemical structure of pyrrolidinium-based ionic liquids and their corresponding ionic liquid homopolymers. B) Synthesis of pyrrolidinium-based ionic liquid homopolymers C) Growth curves of bacteria incubated with pyrrolidinium-based ionic liquids and the corresponding ionic liquid homopolymer solutions applied at each agent's minimum inhibitory concentration (MIC) against *E. coli* I, III) and *S. aureus* II, IV). Ionic liquid monomers and ionic liquid homopolymers with longer alkyl chains had lower MIC values and more potent antibacterial properties against both bacteria. In addition, ionic liquid homopolymers had relatively lower MIC values compared with small molecule ionic liquids. The results suggest that pyrrolidinium-based ionic liquids and the corresponding ionic liquid homopolymers effectively kill bacteria or inhibit their growth. "R" represents alkyl; RAFT: reversible addition–fragmentation chain-transfer polymerization. Reproduced with permission.[29] Copyright 2017, American Chemical Society.

is highly complex and dynamic, which is governed by multiple biochemical, biophysical, and environmental factors.[92–96] Exposure to infectious agents, especially pathogenic bacteria, is one such environmental factor that adversely affects the healing process and delays the recovery of damaged tissue. Agents with antibacterial properties, such as antibiotics and nanoparticles, have been used in tissue-engineered constructs (e.g., bandages, scaffolds, and hydrogels) in the form of coatings,

encapsulations or functionalization strategies.[97–99] Ionic liquids are biocompatible and possess effective antibacterial properties. They have found applications in the domains of tissue engineering and regenerative medicine.[2,100–102] While the conventional approaches result in an uncontrolled release of antimicrobial agents that produces multiple complications, ionic liquids are essentially nonreleasing.

6.1.1. Dermal Wound Healing Applications

Constant exposure of the skin to the external environment renders it highly susceptible to bacterial infection, especially at a damaged tissue site.[103] The nonreleasing property and antibacterial potency of ionic liquids have recently been exploited to fabricate hydrogel wound dressings using a two-step protocol.[104] First, a hydrogel composing of poly(vinyl alcohol), acrylamide, and 1-vinyl-3-butylimidazolium bromide ([VBIm][Br]) was synthesized using radical polymerization strategy. Then it was subjected to repeated freezing/thawing cycles to induce physical crosslinking between the components. The hydrogels exhibited antibacterial activity that was dependent on the concentration of the polyionic liquid. Besides, they were also effective against fungi and mold. The application of these wound dressing also accelerated the healing rate in murine models with critical cutaneous wounds.

Remnant endotoxin derived from dead Gram-negative bacteria generates inflammatory and pyrogenic responses that delay the wound healing process.[105,106] Cationic polyurethane foams containing different amounts of ionic liquid (1,3-bis(2-hydroxyethyl)imidazolium bromide) have been developed to address this issue.[107] All the foams possessed a strong antibacterial activity against *E. coli*, *S. aureus*, and *Pseudomonas aeruginosa*; however, antibacterial activity was highly dependent on the ionic liquid concentration. Because of their cationic nature, foams also exhibited endotoxin adsorption properties, with >95% lipopolysaccharide (extracted from *P. aeruginosa* PAO1) absorption within 60 min of incubation. The foams were biocompatible, hemocompatible, and supported better healing of dermal wounds with a lower inflammatory response.

Because skin tissue is highly prone to recurring mechanical stress and injury, lignin/polyionic liquid-based, mechanically robust, self-healing, nonreleasing hydrogels were fabricated to address this issue.[108] The hydrogels exhibited excellent bactericidal activity against *E. coli* and *S. aureus* even after repeated usage. The dressings were biocompatible and aided in accelerated healing of dermal wounds in a rat model (**Figure 10**).[108]

The interest of the research community in exploring smart materials has opened up a multitude of avenues in tissue engineering.[109,110] Smart materials are those that respond to one or more stimuli, such as pH, temperature, light, electrical/magnetic fields, glucose, and biological/biochemical factors. This helps to extend tissue microenvironmental control into the fourth dimension, that is, time.[111,112] For example, polyvinyl alcohol-tetrahydroxyborate anion ($B(OH)_4^-$) smart hydrogels supplemented with pyrrolidinium ionic liquid (C_nMPBr) were synthesized using an equimolar mixture of 1-methyl pyrrolidine and 1-alkyl bromide $C_nH_{2n+1}Br$ (length of the alkyl chain $n = 4$, 6, 8, or 12)) (**Figure 11**).[101] Because of its dynamic network connections, the hydrogel exhibited self-healing property and multi-responsiveness (i.e., glucose and pH). The inclusion of ionic liquid resulted in potent antibacterial activity, making the hydrogels valuable as dermal wound dressings.

6.1.2. Dental Applications

Similar to skin, the oral cavity is also a site with a high microbial load.[113] Colonization of bacteria results in lowering pH via the production of lactic acid. The lactic acid, in turn, causes demineralization of tooth enamel.[114] Plaque biofilm colonization often occurs at an orthodontic or periodontic wound site, or on the surface of fixed orthodontic appliances, compromising treatment efficacy.[113,115] To address this issue, an antibacterial orthodontic adhesive has been formulated using a combination of bisphenol A glycidyl methacrylate, triethylene glycol dimethacrylate, colloidal silica, and [BMIm][NTf_2] (an ionic liquid).[102] The composite showed potent antibacterial activity against *Streptococcus mutans*, a major contributor to tooth decay, depending upon the ionic liquid concentration. The composite was nontoxic to human keratinocytes.

Titanium is one of the most commonly used materials for dental implants. In its pristine form, titanium elicits severe inflammatory responses and does not mitigate implant-related infection. Hence, strategies have to be developed for coating pure titanium implants.[116,117] Recently, dicationic imidazolium-based, antimicrobial ionic liquids with amino acid anions, namely, 1,10-bis(3-methylimidazolium-1-yl)decane diphenylalanine (IonL-Phe) and 1,10-bis(3-methylimidazolium-1-yl)decanedimethionine (IonL-Met), were used to coat titanium dental implants. Their compatibility was evaluated in a rat model (**Figure 12**).[118] The study highlighted the effectiveness of the coatings. Coating uniformity was depended on the ionic liquid's nature and concentration, with the IonL-Met coating being a better candidate. The developed implants neither interfere with the wound healing process nor did they induce any foreign body response.

Retention of a carrier system at the target site is often necessary to support its therapeutic outcome. Two different [BMIm][PF_6]-incorporated and chitosan-modified carrier nanosystems have been developed recently. These nanosystems were composed of either poly(D,L-lactide-*co*-glycolide) (PLGA) (in the presence of different surfactants) or polyvinyl caprolactam (PVCL)–polyvinyl acetate (PVA)–polyethylene glycol graft copolymer (Soluplus, Sol) as base materials.[119] Apart from reasonable antimicrobial activities, the nanocomposites were noncytotoxic and were well retained within the periodontal tissues in a murine model. These nanocomposites have the potential for the prevention and early treatment of periodontal disease.

6.1.3. Orthopedic Applications

Injured bone tissue is prone to bacterial infection. Hence, scaffolding materials with antibacterial properties are highly desirable.[120] Ceramic-based materials such as hydroxyapatite and calcium phosphate materials are known to create an osteoinductive and osteoconductive microenvironment to enhance bone defect healing,[121–123] but they often lack

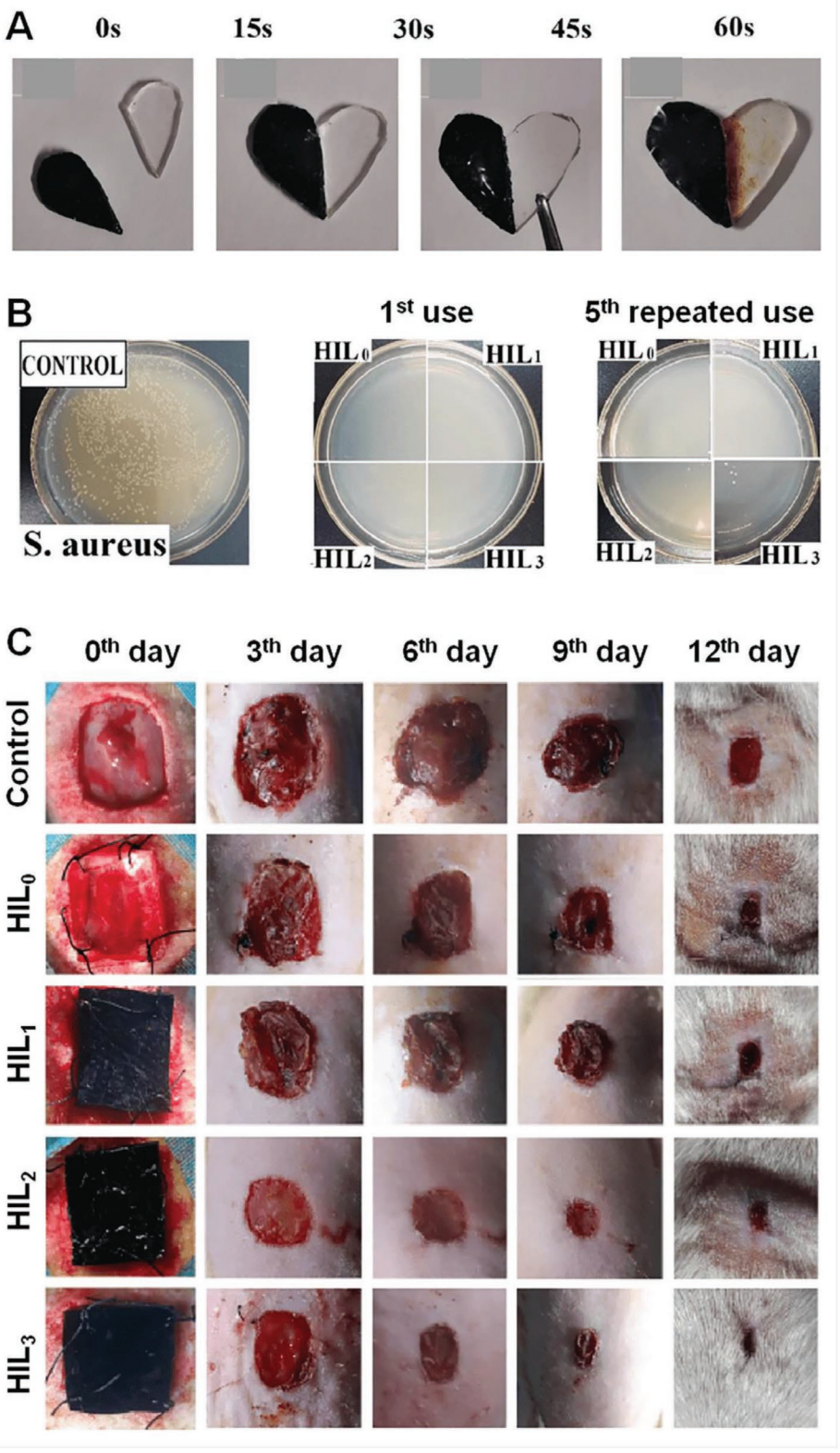

Figure 10. Application of polyionic liquids for dermal tissue engineering. A) Representative images demonstrating the self-healing property of lignin/polyionic liquid. Transparent and black opaque hydrogels represent HIL_0 and HIL_3 specimens, respectively. B) Antibacterial activity of lignin/polyionic liquid hydrogels (HIL_0, HIL_1, HIL_2, and HIL_3 specimens) against *S. aureus*, even after repeated usage. The control set was not exposed to any hydrogel. C) Dermal wound healing of rats after applying the lignin/polyionic liquid hydrogels in a rat model. The control set was not exposed to a hydrogel. The HIL_3 set showed better healing than other hydrogel formulations. The HIL_0, HIL_1, HIL_2, and HIL_3 hydrogels contained 0%, 20%, 40%, 60% lignin methacrylate, respectively. Each set also contained 10% hydroxyethyl methacrylate, 1% [VBIm][Br] ionic liquid and 0.3% azobisisobutyronitrile initiator. Reproduced with permission.[108] Copyright 2020, Elsevier.

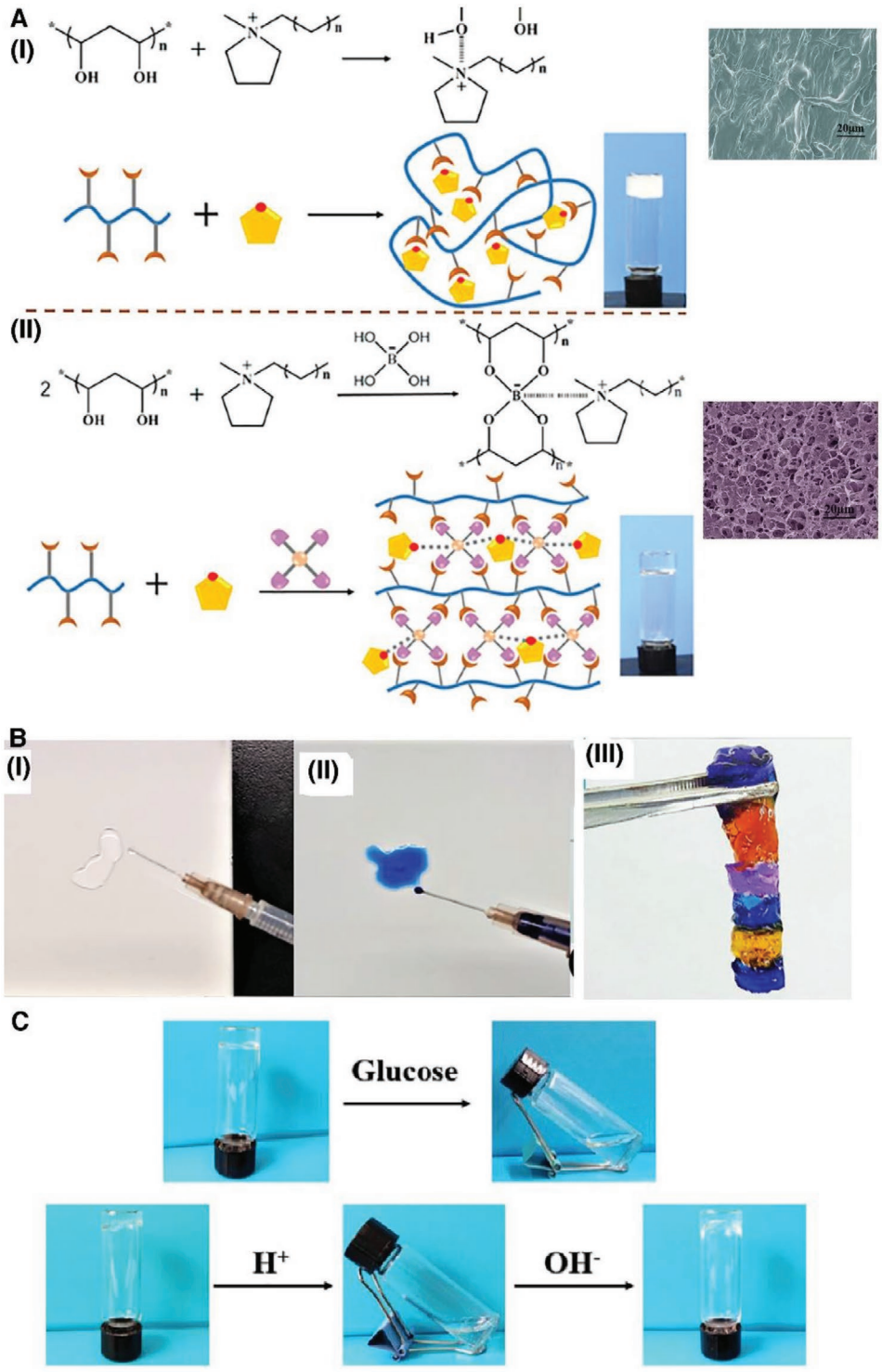

Figure 11. Ionic liquid-based stimuli-responsive hydrogels. A) Schematic demonstrating the mechanism of formation of I) PVA/C_4MPBr and II) PVA/C_4MPBr/$B(OH)_4^-$ along with their representative scanning electron microscopy images. B) Representative images showing reliability, injectability, and self-healing property of PVA/C_4MPBr/$B(OH)_4^-$ hydrogels. I) mixed solution of C_nMPBr and $B(OH)_4^-$ 0.5 mol L^{-1}); II) PVA solution (5 wt%); III) self-healed small hydrogel blocks to form the self-supporting hydrogel. C) Representative images demonstrating glucose-responsiveness and pH-responsiveness of the PVA/C_4MPBr/$B(OH)_4^-$ hydrogels. Reproduced with permission.[101] Copyright 2020, Elsevier.

antibacterial effects. In this regard, loading these materials with ionic liquids may be a feasible approach. For example, injectable calcium phosphate-based nanocomposites have recently been developed using different imidazolium ionic liquids (1-*n*-hexadecyl-3-methylimidazolium chloride ([C_{16}Mim][Cl]), 1,3-di-*n*-decyl-2-methylimidazolium chloride

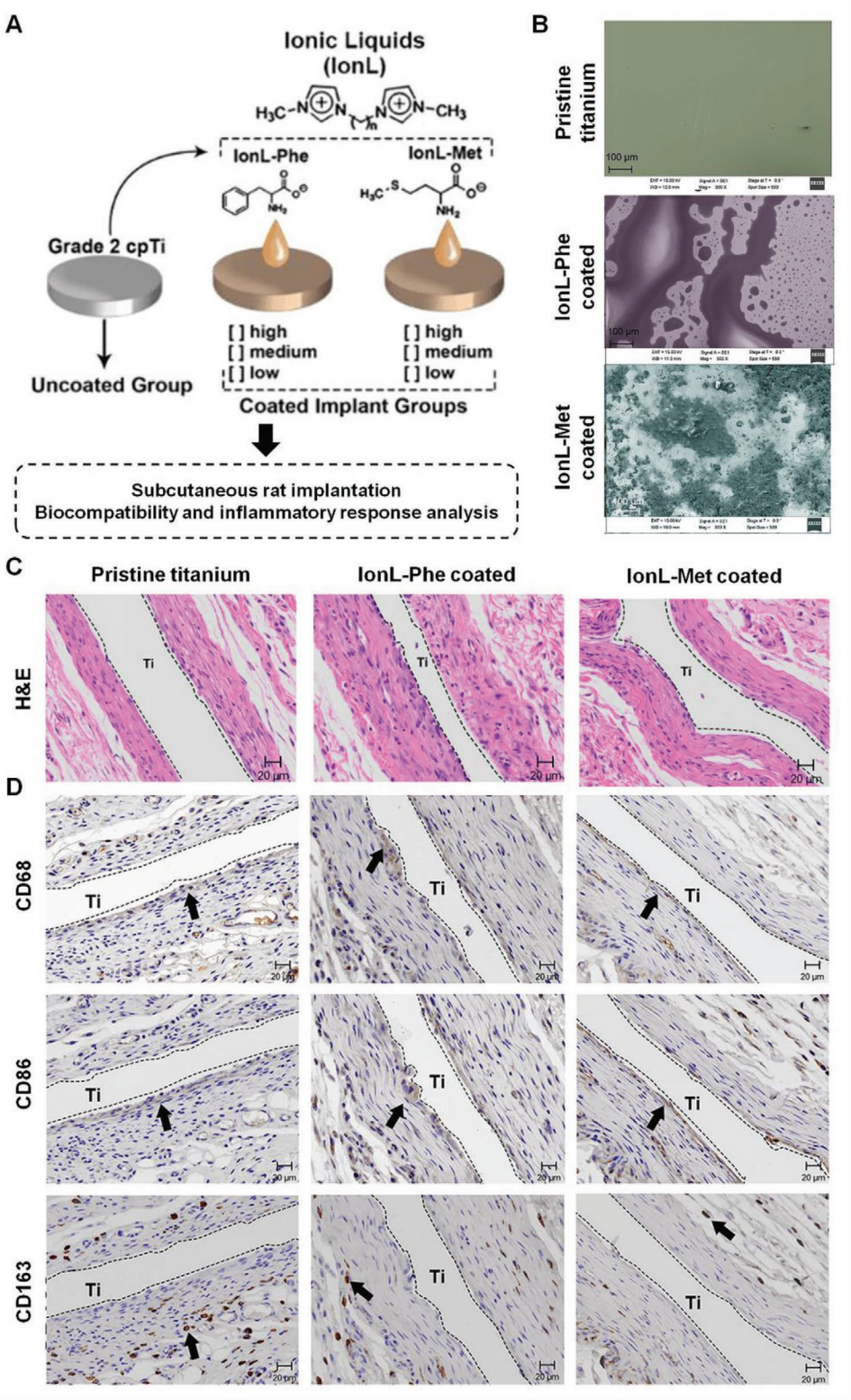

Figure 12. Ionic liquid-coated titanium implants for dental tissue engineering application. A) Experimental design of ionic liquid-coated titanium (Ti) implants. B) Scanning electron microscopy images of pristine and IonL-Met/IonL-Phe-coated Ti implants. C) Hemotoxylin and eosin staining of the coated and uncoated Ti implants and the surrounding tissues. The images represent healing efficacy at 14 days post-implantation. Scale bar: 20 µm. D) Immunohistological staining of the coated and uncoated Ti implants and the surrounding tissues. The images represent inflammatory responses at 14 days post-implantation. CD68, CD86, and CD163 represent universal macrophage markers, M1 macrophage markers, and M2 macrophage markers, respectively. Scale bar: 20 µm Reproduced with permission.[118] Copyright 2020, American Chemical Society.

Table 2. Antibacterial ionic liquids for wound healing and tissue regeneration applications. Abbreviations: bisGMA: bisphenol A glycidyl methacrylate, GO: graphene oxide, HEMA: 2-hydroxyethyl methacrylate, MRSA: methicillin-resistant *Staphylococcus aureus*, PLGA: poly(lactic-*co*-glycolic acid), PVA: polyvinyl alcohol, TEGDMA: triethylene glycol dimethacrylate.

Ionic liquids (IL)	Polymeric components	Antibacterial activity against	Application	Impact on tissue regeneration	Ref.
Pyrrolidinium ILs	Acrylonitrile, styrene	*E. coli*, *S. aureus*	Dermal	Developed composites were biocompatible.	[29]
1,3-Bis(2-hydroxyethyl) imidazolium bromide	Polypropylene glycol	*E. coli*, *S. aureus*, *P. Aeruginosa*	Dermal	Developed composite was biocompatible and promoted the growth of cells. Improved the survival of mice with infected wounds along with the generation of low inflammatory response. Scaffolds also absorbed lipopolysaccharide.	[107]
Quaternary ammonium- or imidazolium-ILs	Acrylonitrile, styrene (with/without immersion of prepared films in $ZnCl_2$ saturated ethanol)	*E. coli*, *S. aureus*	Dermal	Faster healing with reduced inflammatory response in MRSA-infected wounds. Ionic liquid type and presence/absence of Zn^{2+} ions determined the antibacterial and healing response.	[125]
1-vinyl-3-butylimidazolium bromide [VBIm][Br]	PVA, acrylamide	*E. coli*, *S. aureus*, *B. subtilis*	Dermal	Faster healing of wounds was observed in the composite hydrogels, with response dependent on ionic liquid concentration.	[104]
1-vinyl-3-hydroxylheptylimidazolium bromide [HVIm][Br] (ionic or covalent interaction with amino acids)	Acrylonitrile, styrene	*E. coli*, *S. aureus*, MRSA	Dermal	Faster healing with a reduced inflammatory response in MRSA-infected wounds. Amino acid type, chirality, and nature of the chemical bond (ionic or covalent) determined the antibacterial response.	[126]
1-vinyl-3-butylimidazolium bromide [VBIm][Br]	Lignin, HEMA	*E. coli*, *S. aureus*	Dermal	Faster healing of wounds observed in composite hydrogels. The response was dependent on the concentration of ionic liquid.	[108]
1-vinyl-3-butylimidazolium bromide [VBIm][Br]	Polyethylene glycol dimethacrylate, *N,N*-methylene-bis-acrylamide, methyl methacrylate, and acrylamide	*E. coli*, *S. aureus*	Dermal	Faster healing of wounds observed. Healing was dependent on the concentration of ionic liquid.	[100]
Pyrrolidinium ILs	PVA (with/without tetrahydroxyborate anion)	*E. coli*, *S. aureus*	Dermal (proposed)	–	[101]
3-(3-(trimethoxysilyl) propyl)-1-vinyl-1H-imidazol-3-ium chloride (grafted on GO)	Poly-D-lactide and poly-L-lactide	*E. coli*, *S. aureus*	Tracheal	Faster tissue regeneration observed in composite electrospun mats.	[127]
1-*n*-butyl-3-methylimidazoilium bis(trifluoromethanesulfonyl) imide ([BMIm][NTf2])	BisGMA, TEGDMA, colloidal silicon dioxide	*S. mutans*	Orthodontic	The developed composite was biocompatible. Concentration of ionic liquid affected its antimicrobial properties.	[102]
1-butyl-3-methylimidazolium hexafluorophosphate ([BMIm][PF_6])	PLGA or Soluplus	*S. epidermidis*	Periodontal	The developed composite was biocompatible. Ionic liquid-containing nanoparticles showed higher retention in the tissue.	[119]
Imidazolium ILs (loaded in calcium phosphate-based nanocomposites)	–	*E. coli*, *S. aureus*	Orthopedic	Viability, growth, and osteogenic differentiation of MSCs, along with reduced inflammatory response were observed.	[124]

([$(C_{10})_2$Mim][Cl]), 1-*n*-butyl-3-methylimidazolium chloride ([C_4Mim][Cl]) and 1-*n*-decyl-3- methylimidazolium chloride ([C_{10}Mim][Cl])) via in situ sol-gel synthesis.[124] The biological properties of the nanocomposites were highly dependent on the type and concentration of the ionic liquid used. Calcium phosphate loaded with [C_{16}Mim][Cl] or [$(C_{10})_2$Mim][Cl] showed reasonable antimicrobial activity and supported the growth and osteogenic differentiation of human mesenchymal stem cells. In addition, all the ionic liquid-based calcium phosphate-based nanocomposites exhibited potent anti-inflammatory properties.

Table 2 summarizes the recent advancements made with antibacterial ionic liquids in the tissue engineering domain.

6.2. Drug Delivery

Delivery systems are used to sustain and control the release of the loaded contents for improving the efficacy of medical treatment. Ionic liquids are used in delivery systems to confer antimicrobial properties to different types of medical devices without relying on the use of antibiotics. For example, a polymeric nanoparticle drug delivery system has been formulated in which the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM][PF_6]) was incorporated into a base material consisting of PLGA, polyvinyl caprolactam (PVCL), PVA, and polyethylene glycol graft copolymer (Soluplus, Sol).[128] The ionic liquid increased the retention ability of the polymeric

nanoparticles even in the presence of saliva. The ionic liquid also possessed antibacterial activity and caused cracking of bacteria cell walls and cytoplasmic membranes. Incorporating the antibacterial ionic liquid endows the polymeric nanoparticles with potent antibacterial activity without the additional use of impregnated drugs.

Ionic liquids may be combined with drugs to produce drug delivery systems. Ionic liquids that contain imidazolium cations were used to prepare poly(lactic-*co*-glycolic acid)-based, chitosan-functionalized nanoparticles for drug delivery purposes, using the emulsion solvent diffusion method (**Figure 13**A).[129] The resulting nanoparticles possessed strong antibacterial activity against biofilms, as revealed by annular dark-field scanning transmission electron microscopy (Figure 13B,C).

Antibiotics such as ampicillin may be used to prepare ionic liquids in the so-called active pharmaceutical ingredient–ionic liquids, as shown in **Figure 14**. Ampicillin (anion) may be combined with different organic cations to create a tunable library with significant biological variations in their antibacterial activities against Gram-positive (*S. aureus*) and Gram-negative bacteria (*Klebsiella pneumoniae*).[59,130] Development of bacterial resistance toward antibiotics may be overcome by using such an approach. A large number of ionic pairs that can be assembled as an active pharmaceutical ingredient–ionic liquids render this research area particularly interesting. Their facile synthesis methods enable these agents to be produced relatively quickly on an industrial scale, which favors future clinical application.[59]

Ionic liquids with amphiphilic properties may also be employed to form polymeric systems that can load both ionic and nonionic pharmaceuticals for anti-inflammatory and anticoagulant applications.[131] For example, salicylate (anionic drug) may be utilized as a counterion for preparing trimethylammonium poly(meth)acrylates. The self-assembled spherical structures (≈70 nm in diameter) may be used for loading quercetin (nonionic drug), indomethacin (anti-inflammatory drug), and erythromycin (antibiotic).[131]

Ionic liquids may also be used as templates for the preparation of mesoporous silica materials. Mesoporous silica may be assembled with the use of amphiphilic molecules into mesoporous silica nanoparticles (MSN).[132] Ionic liquids released from the MSNs have long-lasting and tunable antibacterial performance against *E. coli*. The release rate of ionic liquids can be tuned by adjusting the particle and pore morphology of the MSNs, using different room temperature ionic liquid templates.[132] Mesoporous silica nanoparticles with ordered hexagonal pores have a faster diffusion rate of ionic liquids when compared to those with disordered pore arrangements; hence, the former possess better antibacterial performance. In addition, mass transfer through tubular pores is slower than through spherical pores. The slower release of ionic liquids results in poorer antibacterial performance.

Apart from conferring antibacterial properties, ionic liquids may also be used as building blocks to produce nanoparticles by introducing electric charges to improve the colloidal stability of the nanoparticles. Ionic liquids may be linked with targeting ligands (e.g., folic acid or hyaluronic acid, light-responsive agents (e.g., *p*-hydroxyazobenzene), or pH-responsive material (e.g., dimethylaminoethyl methacrylate) to prepare self-assembled nanoparticles that are capable of selectively releasing their content (e.g., doxorubicin, an anti-cancer drug) in an optimized manner. Polymerized ionic liquid-based drug-loaded nanoparticles release drug molecules efficaciously to inhibit tumor growth in a murine model. This represents a promising strategy to improve the effects of chemotherapeutic drugs. Similar results may be obtained using *N,N*-dimethylaminoethyl methacrylate-based ionic liquid as a monomer for nanoparticle synthesis. The resulting nanoparticles exhibited good antibacterial activity together with the capacity to deliver doxorubicin for experimental anti-cancer therapy.[133]

Although polymeric particles possess the advantage of selectively releasing their content to optimize drug release rates, there are challenges to be solved prior to commercialization. A major challenge is scaling up for industrial production.

An alternative is to capitalize on electrostatic interaction between the drug molecules and the polymer matrix. This strategy improves the release processes, increases drug stability, and produces a diffusion-driven sustained release profile. This strategy helps to circumvent problems associated with the chemical modification of the drug. The drug-polymerized ionic liquid conjugate may be produced by ring-opening polymerization using ionic liquid as the initiator. The resulting polymer can be subsequently loaded with the drug (mefenamic acid) by taking advantage of the ion-exchange reaction (i.e., the ionic liquid is positively charged while mefenamic acid is negatively charged).

Ionic liquids may also be useful for fabricating stimulus-responsive delivery systems. The advantage of responsive delivery devices resides in the possibility to properly control the release rates of loaded drugs at a designated time. Release of the active molecules occurs not only by uncontrolled diffusion-based mechanisms but also by external or internal triggers. The use of a light source is one of the most promising triggers. Clinicians can easily control light with the absence of toxic effects for patients.[134–136] Although auspicious results have been achieved by researchers, some important issues should be addressed prior to clinical translation. Most importantly, photoresponsive devices have to be optimized for using low energy light output to improve pharmacological efficacy. Intercalation of an azobenzene imidazolium-ionic liquid between montmorillonite layers has been shown to be an extremely efficient strategy. When irradiated by ultraviolet light, azobenzene imidazolium-ionic liquid are capable of altering the distance between montmorillonite layers, acting as molecular jacks (**Figure 15**A). This is achieved by taking advantage of the slightly different dimensions of the cis or trans conformations of an azobenzene imidazolium-ionic liquid, which possess different structural characteristics and molecular properties (Figure 15B). Consequently, drug loading and release rates may be tuned by altering the basal distance of exfoliated montmorillonite clay. The system acts as an efficient photosensitive drug carrier with only a limited release in the absence of irradiation (Figure 15C,D).[137] The light-responsive feature of azo-based materials has been founded as a strategy to efficiently expose higher antibacterial activity under visible light exposure ($\lambda > 400$ nm *trans*-state) than UV light exposure ($\lambda = 300$–400 nm *cis*-state); one can speak of on-off antibacterial materials (Figure 15E). Although in most cases, the antibacterial efficacy of molecules with *trans*-state increases due to the more

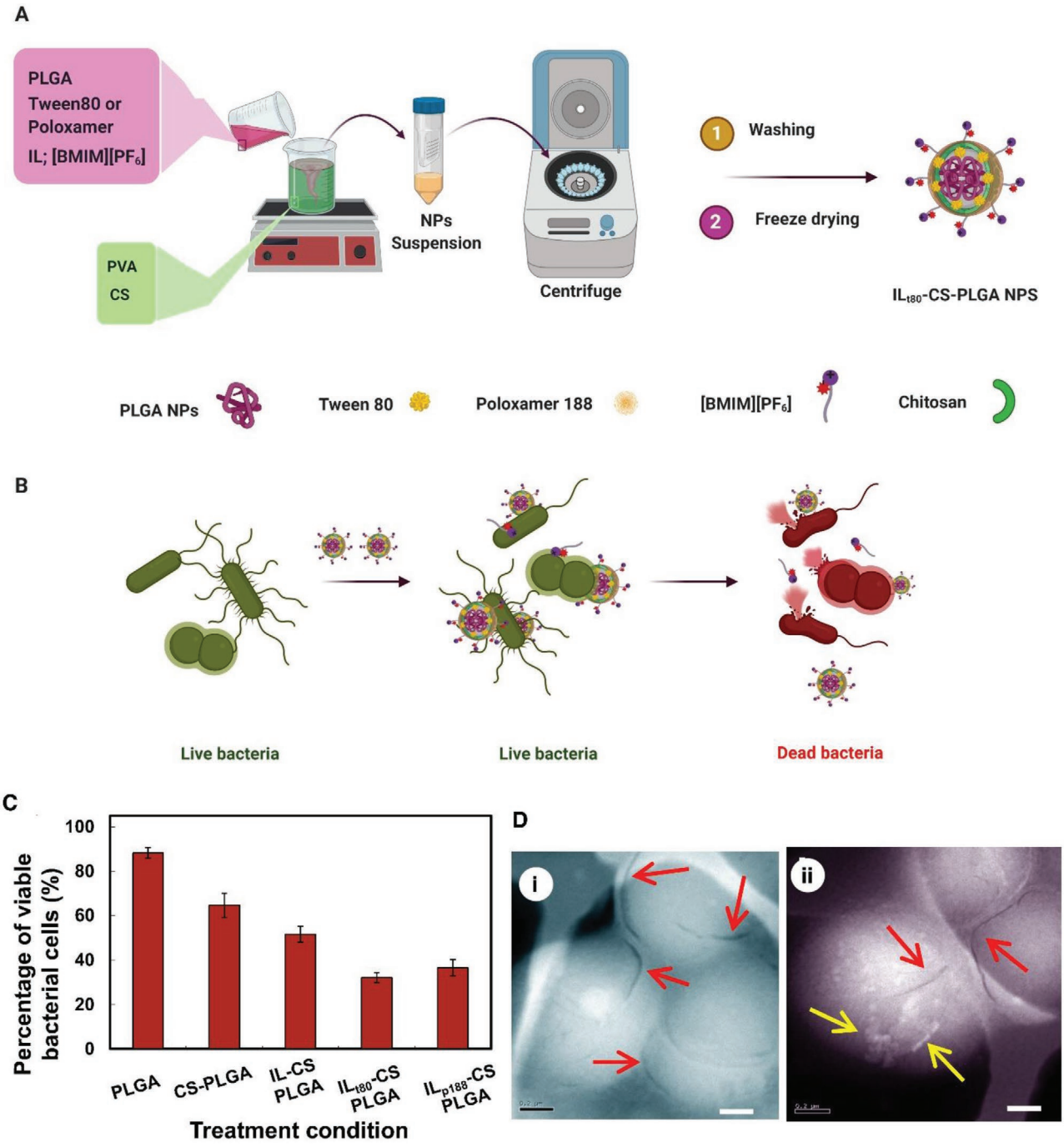

Figure 13. Ionic liquid (IL)-loaded chitosan-functionalized nanoparticles (NPs) based on poly(lactide-*co*-glycolide) (IL-CS-PLGA) as a platform for delivery of antimicrobial agents. Preparation of IL-CS-PLGA NPs A) and interaction with bacteria B). C) Percentage of viable bacterial cells after treatment with various types of PLGA NPs (1 mg per well). D) Annular dark-field scanning transmission electron microscopy of a biofilm treated with IL$_{t80}$-CS-PLGA NPs i) and IL$_{p188}$-CS-PLGA NPs ii). Red arrows indicate cracks in the bacterial cells. Yellow arrows indicate liquid-like morphology in the bacterial cell. Scale bar: 200 nm. PLGA: Poly(D,L-lactide-*co*-glycolide); CS: chitosan; IL-incorporated PLGA NPs with no surfactant, with Tween-80, and poloxamer-188 were named IL-CS-PLGA NPs, ILt80-CS-PLGA NPs, and ILp188-CS-PLGA NPs, respectively. C,D) Reproduced with permission.[129] Copyright 2019, Elsevier.

availability of their antibacterial agents,[138–140] in some cases, the molecules with *cis*-state perform better than their *trans*-states; particularly the azobenzene groups carry carbohydrate or steroid moieties.[140–142] As well, in this study the intercalated azobenzene groups bearing antibacterial agents (i.e., imidazolium agents) inside the exfoliated montmorillonite nanosheets can act as antibacterial surfaces in *cis*-state (increased montmorillonite basal distance) due to the more availability of agents

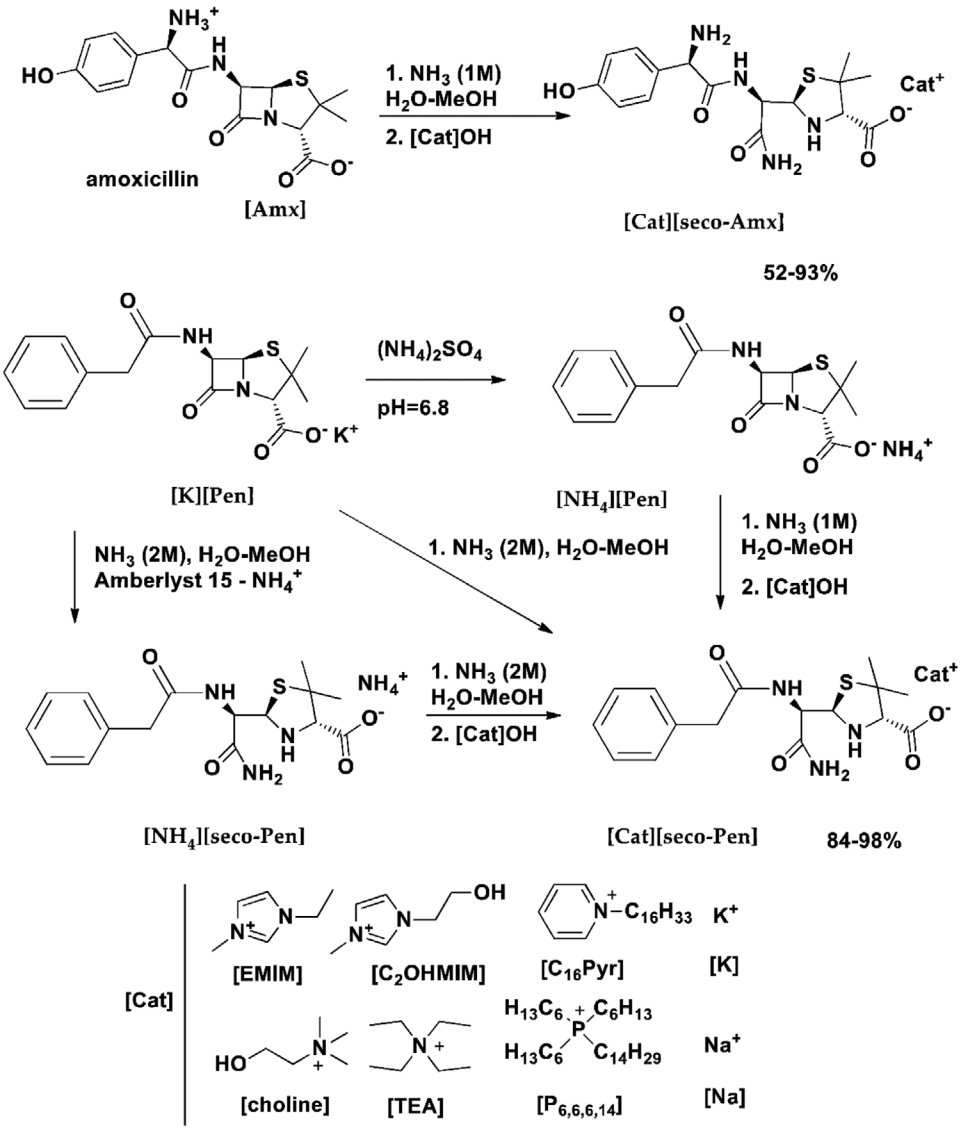

Figure 14. Schematic of the synthesis of active pharmaceutical ingredient (API) salts and ionic liquids. Ionic liquids containing anionic penicillin G [*seco*-Pen] and amoxicillin [*seco*-Amx] hydrolysate derivatives. Reproduced under the terms of the CC-BY license.[59] Copyright 2020, MDPI.

and deactivated in *trans*-state (decreased montmorillonite basal distance).[137] Besides, these nanoplatforms can efficiently deliver antibacterial agents in *cis*-state more than *trans*-state.

7. Trends, Challenges, and Future Perspectives

New aspects of the applications of ionic liquids are being discovered and expanded. Because of the positive charges of ionic liquids and their great affinity for negatively charged surfaces such as bacteria membranes and ionic liquids are used in bioapplications for combating infections. Ionic liquids possess anion exchangeability. Anions with different hydrophobicity may be tailored to tune the bactericidal activities of ionic liquids. Depending on how and where they are deployed, antibacterial ionic liquids may be utilized as monomers, polymers, surfactants, or membranes.

Scientists have been exploring green alternative solvents instead of volatile organic solvents to synthesize ionic liquids. The nonvolatile and nonflammable solvents utilized in green chemistry have minimally damaging effects on atmospheric photochemistry.[143] Ionic liquids synthesized via green chemistry can be employed in the separation/purification and extraction of bioactive compounds such as proteins, amino acids, nucleic acids, lipids (fats, essential oils, carotenoids, saponins, vitamins), pharmaceuticals, and drugs.[144] Ionic liquids may be used under vacuum conditions because of their negligible volatility. The thermal stability and nonflammability of ionic liquids are additional features that render them exceptionally safe for the fabrication of electrochemical biosensors. Apart from their common use as biocatalysis, in electrochemical devices, and as engineering fluids, ionic liquids gradually find to be used in the medical and biological arena. For example, ionic liquid-based electrochemical biosensors have been developed for detecting

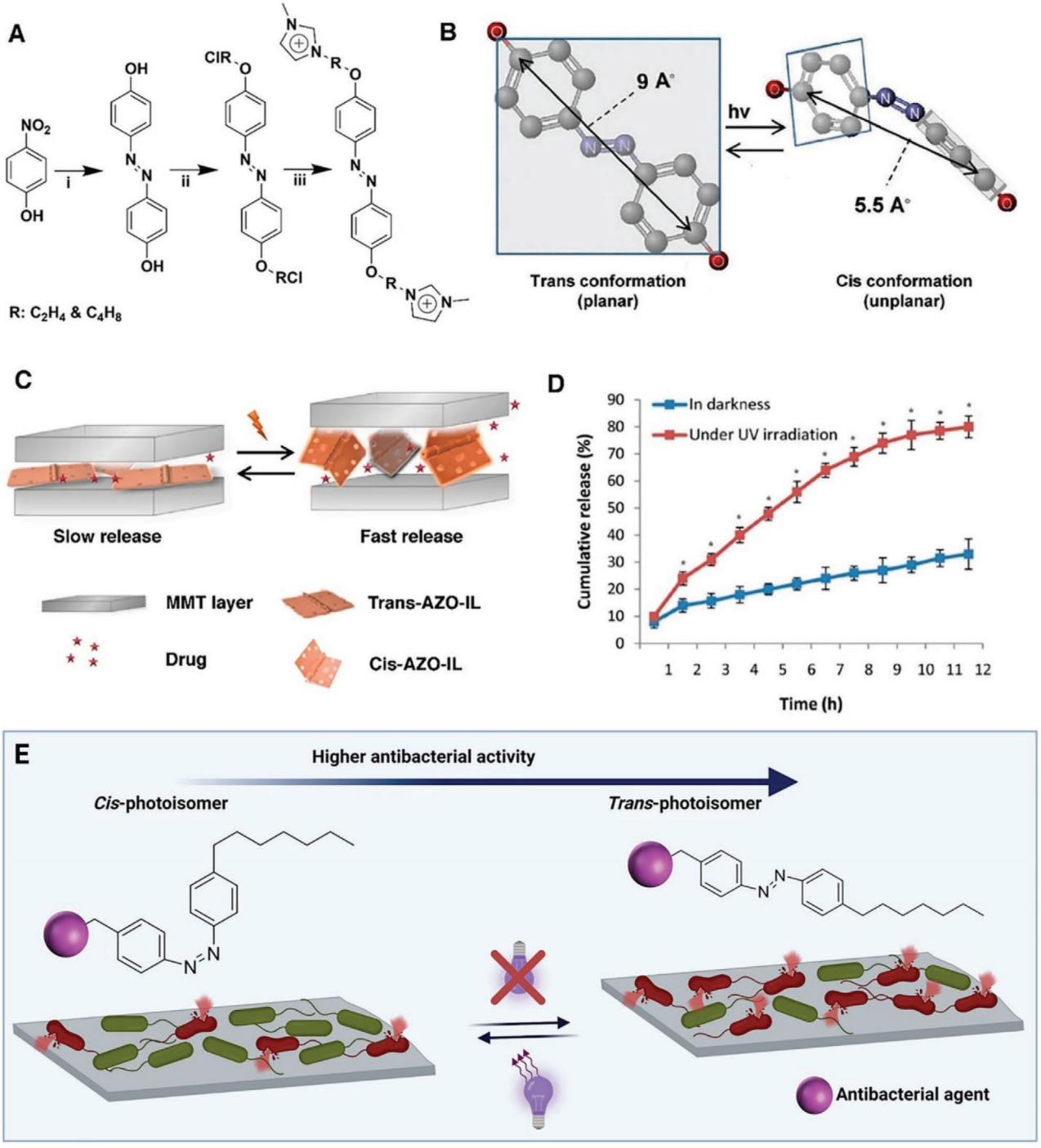

Figure 15. Light-responsive drug delivery nanoplatform containing azobenzene imidazolium ionic liquid acting as molecular jacks. A) Synthesis of 4,4′-bis(2-ethoxymethylimidazolium)azobenzene ionic liquid (Azo-ILs). B) Switching the molecular jacks from the cis-state to the trans-state alters the basal distance between exfoliated montmorillonite (MMT) clay layers and creates room for drug-loaded (release triggered by ultraviolet light radiation). C) Schematic of the intercalation between Azo-ILs and MMT layers D) In vitro release profiles of *para*-aminobenzoic acid in the dark (blue) and upon ultraviolet light radiation (red). Reproduced with permission.[137] Copyright 2018, American Chemical Society. E) Schematic illustration on antibacterial activity of *cis*- and *trans*-states of azo molecule. In most cases *trans*-state of azobenzene derivatives containing antibacterial agents perform better than their *cis*-states. However, in this case, it is predicted that the *cis*-state of azobenzene imidazolium ionic liquid acts more efficient than *trans*-state due to the availability of imidazolium cations in the increased basal distance of MMT nanolayers.

bacteria in blood samples. This enables accurate determination of the optimal dosage of antimicrobial drugs for treating a specific infectious disease.

The development of alternative antibiotics or modifying current antibacterial strategies is urgently needed to manage the infection caused by antibiotic-resistance bacteria. Ionic liquid-based therapeutics has immense potential to replace conventional antibiotics in the combat of multidrug-resistant infections. Antibacterial strategies based on ionic liquids are not yet mature for commercial use, and most of them are undergoing preclinical studies.[5,65,145,146] Well-designed and controlled clinical trials should be performed on strategies of potential therapeutic significance in treating pandemic infectious diseases. Despite the existing difficulties in getting approval from the US Food and Drug Administration and the European Medicine Agency, there have been admirable efforts to alter the biological activity of ionic liquid-based antibacterial materials to present these materials as new therapeutic agents against multidrug-resistant bacterial pathogens.[5,65,145,146]

Antimicrobial ionic liquid-based materials have two major competitors: antimicrobial peptides and antimicrobial metal/metal oxide nanoparticles. Although these two competitive materials possess outstanding features, they have limitations that hinder their applications. For instance, antimicrobial peptides are high in their production costs,[147] potentially toxic to humans,[148] sensitive to harsh environmental conditions such as pH and proteases,[149] degradable by tissue proteolytic enzymes, and susceptible to hemolysis due to their hydrophobicity and/or amphipathicity.[150] When they are used for coating surfaces, antimicrobial peptides lose their selectivity toward specific bacterial strains.[151] Besides, the unfolding of some large antimicrobial peptides results in the loss of their antimicrobial activity.[152]

Metal/metal oxide nanoparticles are potentially toxic to normal cells. The size, shape, and composition influence the cytotoxicity and antimicrobial features of metal oxide and metallic nanoparticles.[42] The cytotoxicity of metal/metal oxide nanoparticles limits their biomedical applications. Cytotoxicity is caused by the release of toxic ions, which, in turn, create oxidative stress to the host cells. Ion release is an intrinsic property of these antibacterial nanoparticles and is dependent on the surface charge, particle size, morphology, and surface chemistry.[153] Nonbiogenic synthesis, agglomeration, opsonization, interaction with the monocytes and macrophages, as well as DNA damage caused by the generation of reactive oxygen species are additional drawbacks of antibacterial nanoparticles.[154,155] Although some of these drawbacks may be solved with new green synthesis methods and surface modifications with biopolymers, peptides, and aptamers,[42,156] further studies are required to determine the biocompatibility, cytotoxicity, and antimicrobial efficacy of these green-synthesized nanoparticles. Thus, it appears that antibacterial ionic liquid derivatives are suitable antibacterial agents of the future.

Most antibacterial poly(ionic liquids) and ionic liquid-based membranes are synthesized from vinyl monomers bearing ionic liquid moieties. Hence, the final products are not biodegradable. This is a severe limitation in terms of biomedical applications. To tackle this problem, vinyl poly(ionic liquids) may be blended with biodegradable synthetic polymers (e.g., polycaprolactone, polylactide, polyglycolide, poly(lactide-*co*-glycolide), poly(hydroxy butyrate), poly(butylene adipate) or polyorthoesters), or natural polymers (e.g., alginate, chitosan, carrageenan, hyaluronic acid, gelatin, or collagen) to increase their biodegradability.[157–159] In addition, biopolymers may be structurally modified with ionic liquids.[160–162] Poly(ionic liquids)s consisting of biodegradable segments can also be prepared, for example, via polycondensation of 1,2-bis[*N*-(*N*′-hydroxylalkylimidazolium)]ethane salts with different diacid chlorides; the latter include adipoyl chloride, succinyl chloride, sebacoyl chloride, and terephthaloyl chloride.[163] Such manipulations will enhance the biocompatibility of ionic liquid-based materials. Further studies of the physicochemical and biological properties of these biodegradable ionic liquid-based materials are required to balance antimicrobial efficacy with biocompatibility toward mammalian cells.

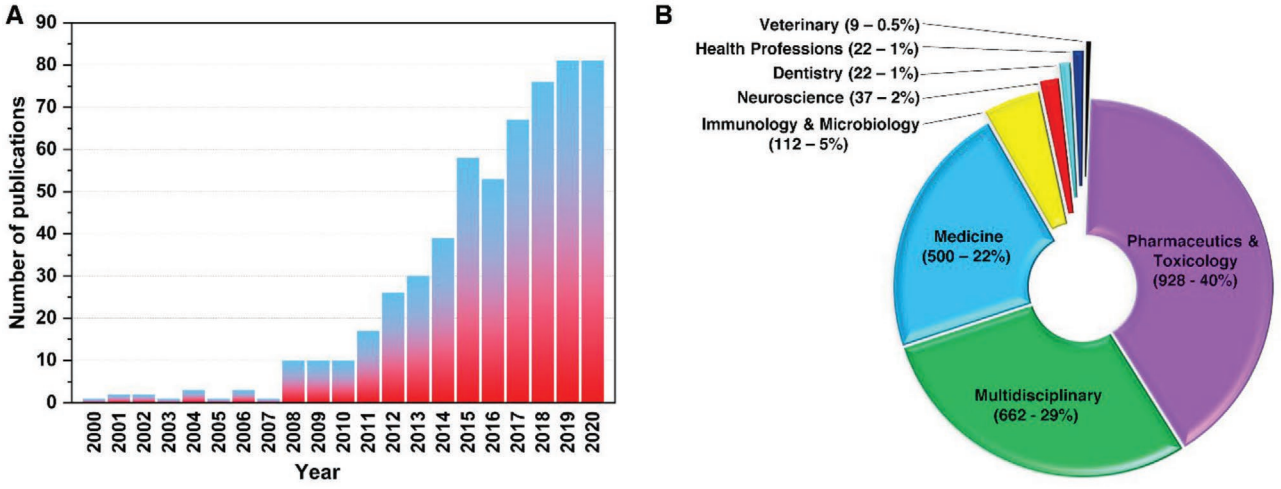

Figure 16. Statistics of published data on biomedical applications of ionic liquid derivatives as antimicrobial agents. A) The number of publications related to the bactericidal effect of ionic liquid derivatives by year of publication. B) The number of publications on the biomedical applications of ionic liquid derivatives; the parentheses' data shows the number of publications and related percentages. Data extracted from Scopus (accessed January 1, 2021).

8. Conclusion

Almost half of the drugs sold in drugstores are salts. Salts that are liquid at body temperature or room temperature have better solubility, stability, and adsorbability when compared with solid salts.[145] Hence, ionic liquids may be designed and configured to deliver at least two active biological agents simultaneously. For example, procainium salicylate is an ionic liquid that delivers a pain-relieving agent (procaine) and a nonsteroidal anti-inflammatory drug (salicylic acid) to the body simultaneously.[145]

Over the past decade, ionic liquids have been mostly ignored due to the lack of understanding and experience of these materials. Pharmaceutical companies consider it too risky to develop, invest, and commercialize ionic liquid-based antimicrobial materials. In recent years, the lack of appropriate antibiotics against multidrug-resistant bacteria has revived scientists' interests and probably those of large pharmaceutical companies pursuing the development of antibacterial ionic liquid derivatives as sustainable, efficient, and economically viable antibacterial agents. This is particularly so when antibacterial resistance is rapidly becoming a global health threat that increases morbidity and mortality. Statistics showed that the number of publications related to the bactericidal effect of ionic liquids has escalated on a yearly basis (**Figure 16**A). These publications include the synthesis of new ionic liquid-based antibacterial agents, ionic liquid-modified surfaces, structural modification of common antibiotics with ionic liquids, and their potential applicability in biomedical research to prevent bacteria-initiated infectious diseases. Among the biomedical applications of ionic liquid derivatives, the ratio of investigations performed on antimicrobial activity is low. Nevertheless, it is anticipated that the number of publications on the antimicrobial effect of ionic liquids will be accelerated in the coming years due to the crucial need to explore and produce alternatives to deal with infections associated with multidrug-resistant bacteria (Figure 16B).

Acknowledgements

M.G. and T.A. contributed equally to this work.

Conflict of Interest

The authors declare no conflict of interest.

Keywords

antibacterial mechanism, chain length, drug delivery, imidazolium, ionic liquid, quaternary ammonium, tissue regeneration

Received: May 1, 2021
Revised: July 1, 2021
Published online:

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