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Ionic Liquids and Its Antimicrobial Activities

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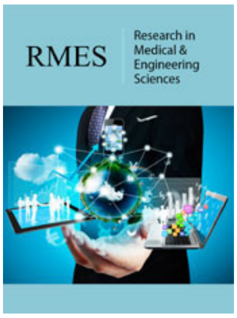

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Abstract

Antimicrobial resistance has become a global health threat, killing more than 10 million human lives annually. Many medical conditions (joint replacements, organ transplants, cancer therapy, and the treatment of chronic diseases like diabetes, asthma, and rheumatoid arthritis) are dependent on a wide range of antibiotics to fight infections. If antibiotics lose their effectiveness due to resistance mechanisms of microbes, we lose the ability to treat infections. To circumvent the issues, the development of novel antibiotic materials is a major goal worldwide. In this scenario, ionic liquid-based antimicrobials are promising. The bactericidal properties of ionic liquids can be tailored by proper selection of ions (cations/anions) during synthesis and optimizing alkyl chain length of cations. Covalent tethering of functional groups on different components of ionic liquid is also practiced globally to impart antimicrobial properties to biocompatible ionic liquids. Current review focused on ionic liquid based antimicrobial strategies.

Keywords: Ionic Liquids; Anions; Cations; Antimicrobial; Antifungal; Antiviral; Antibacterial

Introduction

Ionic liquids (ILs) are magical chemical compounds completely composed of ions with highly tunable characteristics in terms of its chemical structure, and physicochemical properties [1]. ILs has potential applications in the diverse field of modern science including synthesis and catalysis [2], extraction [3], electrochemistry [4], biomedical engineering [5], life sciences [6] and environmental sciences [7] etc. Ethyl ammonium nitrate was the first reported ionic liquid synthesized by Paul Walden in 1914 [8]. At that time, he didn't realize researchers around the world were going to follow his path after a century. High degree of symmetry observed in ILs that affects the ionic packing and reduces the coulombic attraction of ions in it. Initially ionic liquids were used mostly for electrochemical applications; later researchers developed varieties of ionic liquids considering their vast multidisciplinary applications. In the modern era, ILs are divided into many types, e.g., room temperature ILs [9,10], task-specific ILs [11,12], Monomeric ILs [13], Poly ILs [14,15], etc., Some examples of anions and cations used in ionic liquids are given in Figure 1. The physicochemical characteristics of ILs such as high polarity, low volatility and melting point, high thermal stability [16], and ionic conductivity [17] are more promising than conventional organic solvents. The field of ILs are more challenging because of its hybrid nature, which contains both ionic and organic counter parts. The intermolecular interactions in ILs leads to complex phenomena that necessitate thorough understanding of structure-property relationship of ILs in designing task specific applications.

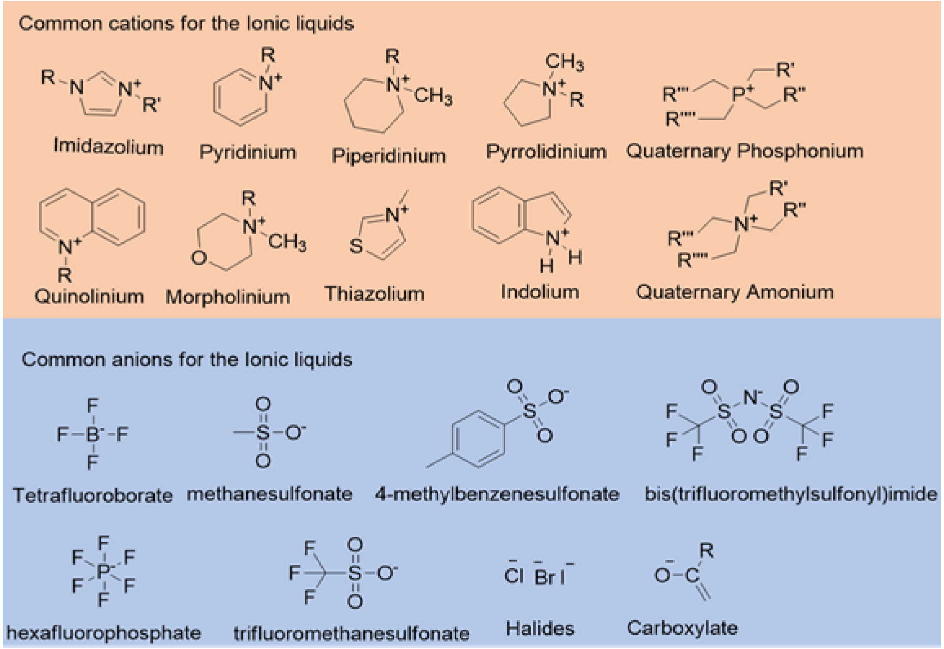

Figure 1: Common cations and anions for the Ionic liquids.

Biomedical applications of ILs are booming with its tunable nature that helps to develop thousands of combinations of biocompatible ILs. The biomedical applications of ILs include drug delivery [18-20], plasticizers [21,22], tissue engineering [19,23,24], cancer therapy [25-27], antimicrobial activity [28,29], and biomedical sensors [30].

Antimicrobial resistance has become a global health concern and the current scenario of covid-19 accelerates its speed. The new resistance mechanisms acquired by drug resistant microbes continue to threaten our ability to treat common infections. According to the World health organization, antimicrobial resistance may cause the death of more than 10 million human life annually by 2050 [31]. Rapid global spread of drug resistant pathogens (superbugs) necessitates new antimicrobials to circumvent the deadly situation. ILs can be a potent candidate to fight against superbugs. Antimicrobial properties can be introduced in ILs by carefully choosing the ions during synthesis. The high surface activity of ILs can react with microbial cell walls disrupting the cell membrane integrity like a biocide. Current review focused on ILs based antimicrobial activities such as antibacterial [28,29,32], antifungal [33-35], and antiviral activities [36-38].

Antibacterial activities of ILs

The ionic liquids containing cationic species such as pyridinium, imidazolium, piperidinium etc., were shown significant antimicrobial properties. Jeong et el. [39], studied the mechanism of interactions of ionic liquid and lipid bilayer using model cell membranes. According to the study, ionic liquids are capable of interfering with cell membranes via alkyl chains and cause cell death. Two possible interactions of IL on lipophilic cell membrane are shown in Figure 2. In the first mechanism, ILs form a nice coating on the cell surface. But the proposed model is useful if the cell surfaces are in neutral form, as zwitterions. In the second mechanism, the hydrophobic tails of the ILs are incorporated into the cell membrane and thereby perturbing cell membrane structure as shown in Figure 2b. The study also discussed the direct correlation of alkyl chain length and concentration of ILs in effective lipid bilayer penetration. In another study, Iwai et al. [40], discussed the antimicrobial activities of imidazolium, pyrrolidinium and piperidinium salts. The study correlates the antimicrobial effect with alkyl chain length and molecular weight of ILs especially made of imidazolium, pyrrolidinium and piperidinium salts. Inhibition of cell division is also proposed for the antimicrobial effect of imidazolium based ILs in the study. Carson et al. [34], demonstrated the broad spectrum of antimicrobial/antibiofilm activity of 1-alkyl-3-methylimidazolium chloride based ILs against a panel of pathogen microorganisms including clinical isolates of MRSA, pathogens associated with hospital-acquired infections. Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of a range of 1-alkyl-3-methylimidazolium chloride ILs with number of carbon atoms in the alkyl group, n=6, 8, 10, 12 and 14 were analyzed using different bacterial strains in the study. The study also showed that minimum biofilm eradication concentration (MBEC) properties of ionic liquids decrease with increase in alkyl chain length of ILs. Santos et al. [29], reported the preparation of ionic liquid from antibiotics such as norfloxacin and ciprofloxacin as anions with enhanced antimicrobial activity. According to data comparison study ionic liquid – antibiotic formulations are promising as they are highly active against both gram negative and gram-positive bacteria. Several studies confirmed that the antimicrobial activity of ionic liquids depended on multiple factors such as alkyl chain length, charges of anions and cations, chemical composition of the anion and cation etc.

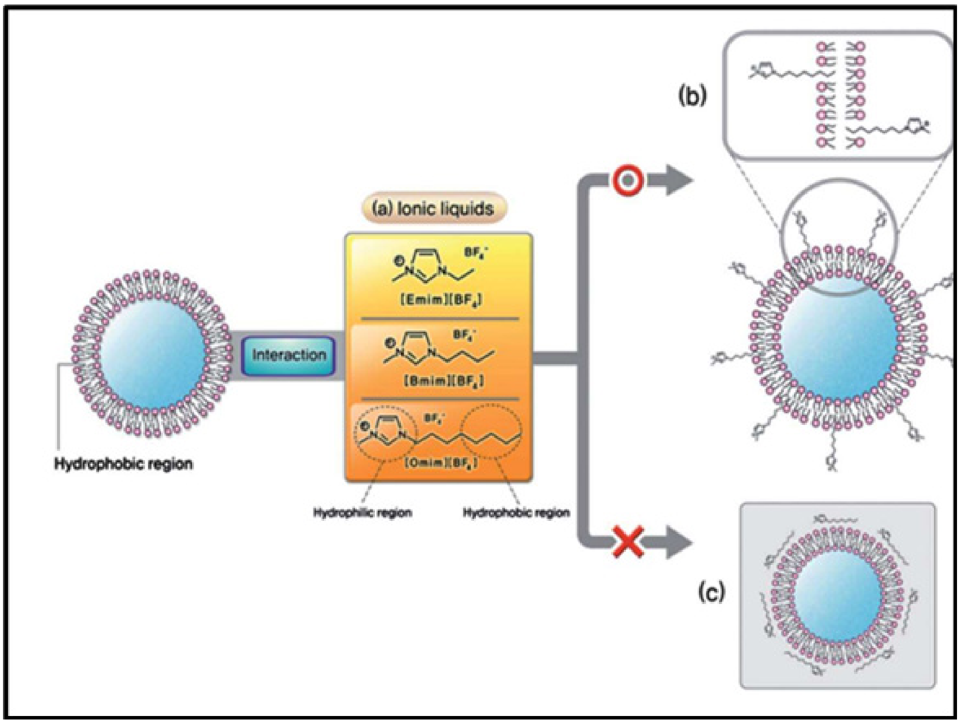

Figure 2: Schematic model of molecular interactions between ILs and lipid membrane [adapted from Jeong et al. [39], with permission from © 2023 Copyright Clearance Center].

Antifungal activities of ILs

Ionic liquids showed excellent fungicidal properties. Mankiewicz et al. [41], studied antibacterial and antifungal effects of quaternary ammonium azolate-based ionic liquids. The study demonstrated that the antimicrobial effect of that ionic liquid is very high compared to the antimicrobial effect of benzalkonium chloride. Mehmood et al. [42], studied the inhibitory effects of 1-ethyl-3-methylimidazolium acetate and 1-ethyl-3-methylimidazolium methyl phosphonate on Saccharomyces cerevisiae. The study demonstrated that residual ionic liquids cause a metabolic switch from respiration to fermentation at higher concentrations of ionic liquids and inhibit the growth of the yeast. Bica et al. [43], developed an ionic liquid with fungicidal effects such as thiabendazole and imazalil to protect the potato from potato tuber disease. Reddy et al. [44], studied the antifungal effect of alkylimidazolium ionic liquids. They also showed the antibiofilm activity of alkylimidazolium ionic liquids against Candida albicans was also demonstrated in the study.

Antiviral activities of ILs

Antiviral activities of Ionic liquid are getting a lot of attention from the global community. A computational study by Palanisamy et al. [36], demonstrated the effect of ionic liquids to inhibit the Mpro of SARS-CoV-2. They studied the molecular docking of biocompatible choline-based ionic liquids against main protease, the salient enzyme in coronavirus. The structural stabilization studies were conducted in 30 choline-based ionic liquids depending on the biological activities and screened ionic liquids based on protein-ligand binding, which may be useful in drug development for Covid-19. Faisca et al. [37], developed an ionic liquid-based effective antiviral compound from hydroxychloroquine. Authors studied strains of SARS-CoV-2 with ionic liquid-modified hydroxychloroquine such as N4 -(7-chloroquinolin-4-yl)-N1 -ethyl-N1 -(2-hydroxyethyl)pentane-1,4-diaminium bis(methanesulfonate) and N4 -(7-chloroquinolin-4-yl)-N1 -ethyl-N1 -(2-hydroxyethyl)pentane-1,4-diaminium bis((2S,3R,4S,5S)-2,3,4,5,6-pentahydroxyhexanoate), [HCQH2][GlcCOO]2, which showed enhanced antiviral activities compared to drug molecules. Moshikur et al. [45] synthesized an ionic liquid-based drug formulation in favipiravir composed of favipiravir as an anion and ionic liquid as a cation. The formulations showed excellent thermal properties. The synthesized formulations showed high aqueous solubility (78-fold higher than the parent drug molecules), bioavailability, pharmacokinetics, and pharmacodynamic properties. Different studies demonstrated the use of ionic liquid as a potential candidate for antiviral drug formulations.

Conclusion

The biomedical applications of ionic liquids showed a consistent growth in the last two decades. Antimicrobial activity of ionic liquid got major attention in this era of ‘Superbugs’. Among different strategies adopted to develop new materials to fight pathogenic microorganisms, ionic liquid-based strategies are more promising. Task specific selection of anion and cation combinations for the synthesis of ionic liquid is a major advantage in this field. Many studies showed a direct correlation of alkyl chain length of cations and antimicrobial activities of corresponding ionic liquids. Importantly, as the alkyl chain length increased, minimum inhibitory concentration (MIC) and minimum bactericidal concentration

(MBC) of corresponding ionic liquids decreased. It was also recommended to use stimulation studies and other computational analysis to select anions and cations or their combinations to impart desired antimicrobial properties on ionic liquids and to promote ionic liquid based antimicrobial technologies to circumvent global health threat related to antimicrobial resistances.

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