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# Ionic Liquids as an Antimicrobial Agent

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**ABSTRACT:**
One of the greatest "miracles" of the 20th century was the development of antibiotics. Due to the growing issue of microbial resistance to conventional antimicrobials and the pharmaceutical industry's lack of investment in novel antimicrobial agents, the marvel of the 20th century's post-antibiotic era is now turning into a nightmare. Unfortunately, the current COVID-19 pandemic has emphasised the dangers of uncontrolled infections on a global scale as well as the various effects that a pandemic may have on the economy and social customs, in addition to the related morbidity and mortality.
As a result, it is important to recycle antimicrobial compounds, as is the case when using ionic liquids (ILs) that are antimicrobial-based. Thus, the aim of the current review is to provide a summary of the information on ILs, primarily those that have antibacterial action, particularly against resistant strains. The primary takeaways from this article are that ILs are adaptable due to their capacity to modify cations and anions as a salt, allowing for the combination of both groups' characteristics and the multiplicative activity of individual cations and anions. Additionally, these compounds may be produced at a low cost, which makes it very appealing to investigate them, particularly as antibacterial agents and against resistant strains. ILs could further develop using a variety of therapeutic approaches, therefore
In order to control uncontrolled infections, they may be able to be used in novel ways.
**KEYWORDS**: ionic liquids; resistance; antimicrobial agents; infection

## I. INTRODUCTION:

Over the past several years, antibiotic-resistant bacteria have become more prevalent throughout Europe [3]. Recent years have not seen the introduction of new classes of antibiotics [4][5], and as a result, resistance to older medications is increasing everyday [6]. Recent efforts and huge investments being made in this field by big pharma companies such as GlaxoSmithKline, Merck, Pfizer and Wyeth [7] [8] have had disappointing returns from their R&D departments, including clinical trials. This is a significant factor to allocate anti-infective R&D resources into other fields of investigation and thus remain highly competitive. Considering the disappointing results on genomics and the exodus of big pharma, the problem of bacteria resistance has continued to evolve, reaching alarming dimensions. [1] Therefore, there is an increasing demand to develop new drugs to address multi-resistant infections and to develop more efficient tools so that new resistances are not developed. [1]

## ANTIMICROBIAL RESISTANCE AND ITS GLOBAL SPREAD

A surveillance study published by the European Centre for Disease Prevention and Control in 2009 demonstrated that approximately 400,000 patients from 28 European countries suffered from infections because of strains of antibiotic-resistant bacteria, with Escherichia coli and Klebsiella pneumoniae being the most common causative pathogens. The proportion of third-generation cephalosporin-resistant E coli increased significantly from 1.7% in 2002 to 8% in 2009, whereas the proportion of E coli isolates with resistance to four classes of antimicrobials increased more than 5-fold from 0.6% in 2002 to 3.4% in 2009. The increase in antibiotic resistance among K pneumoniae is even direr. The European Centre for Disease Prevention and Control reported that the rate of resistance of K pneumoniae to powerful and last-line antibiotics, namely carbapenems, increased from less than 1% to more than 25% in the European Union, 2009.

The prevalence of MDROs in hospitals and medical centers in the USA has also increased steadily during the previous decade [9] [10] [11]. For example, the prevalence of imipenem-resistant Acinetobacterbaumannii infection increased from 4.8% in 2000 to 21% in 2009, and the prevalence of methicillinresistantStaphylococcus aureus (MRSA) increased from 19% in 2000 to 51.5% in 2009. The rate of resistance of E coli to trimethoprim-sulfamethoxazole increased from 17.4% in 2000 to 23.9% in 2009, and that of E coli

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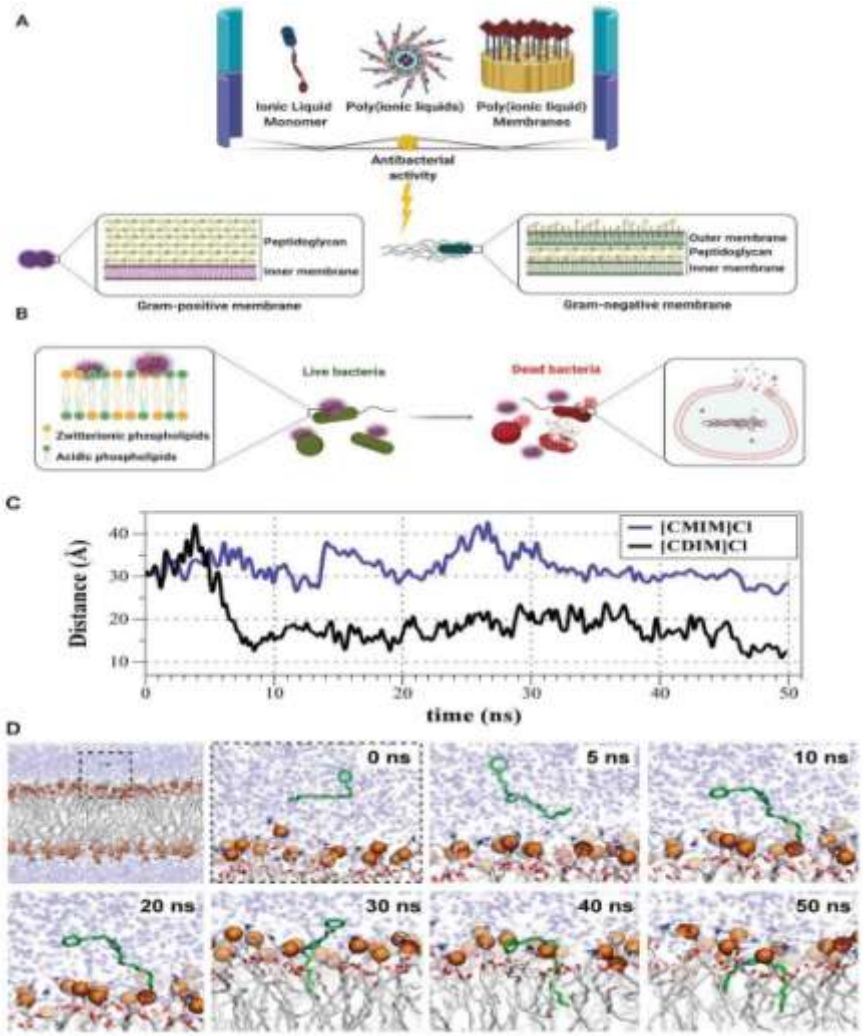
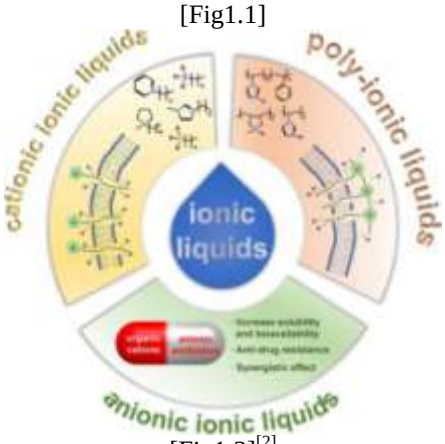
to fluoroquinolones rose from 3.3% in 2000 to 17.8% in 2009. Furthermore, the prevalence of vancomycinresistant enterococci (VRE) isolates has also increased markedly. [9]For example, VRE isolates accounted for 25% and 28.5% of all nosocomial infections in intensive care units (ICUs) in 1999 and 2003 respectively. [9] [3]




[Fig1.1]




[Fig1.2][2]

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**EXAMPLES**

**[Table 1]**

| cation | anion | Microrganisms | Authors and year of publication |
|---|---|---|---|
| didecyldimethylammonium, benzalkonium | lactate | Micrococcus luteus, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus mutans, Enterococcus faecium, Moraxella catarrhalis, Escherichia coli, Serratia marcescens, Proteus vulgaris, Pseudomonas aeruginosa, Bacillus subtilis | [14] |
| didecyldimethylammonium, benzalkonium, cetylpyridinium, 3-hydroxy-1-octyloxymethylpyridinium | saccharinate, acesulfamate | Enterococcus faecium, Escherichia coli, Micrococcus luteus, Staphylococcus epidermidis, Klebsiella pneumoniae Micrococcus luteus, Staphylococcus aureus, | [15] |
| didecyldimethylammonium, benzalkonium, domiphen | mandelate, prolinates | Enterococcus faecium, Serratia marcescens, Proteus vulgaris, Pseudomonasaeruginosa, Bacillus subtilis | [16] |
| 1-alkyl-3-methylimidazolium, alkylpyridinium | chloride, bromide | Staphylococcus aureus, Bacillus subtilis Escherichia coli | [17] |
| chlorhexidine | ampicillinate, carbenicillinate, cephalothinate, oxacillinate | Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus faecalis, Bacillus cereus Enterococcus faecium | [18] |
| 3-cinnamyl-1-alkyl-imidazolium | chloride | Staphylococcus aureus, Streptococcus pyogenes, Staphylococcus epidermidis, Escherichia coli, Pseudomonas aeruginosa, Acinetobacterbaumannii Staphylococcus aureus, Bacillus pumilis, | [19] |

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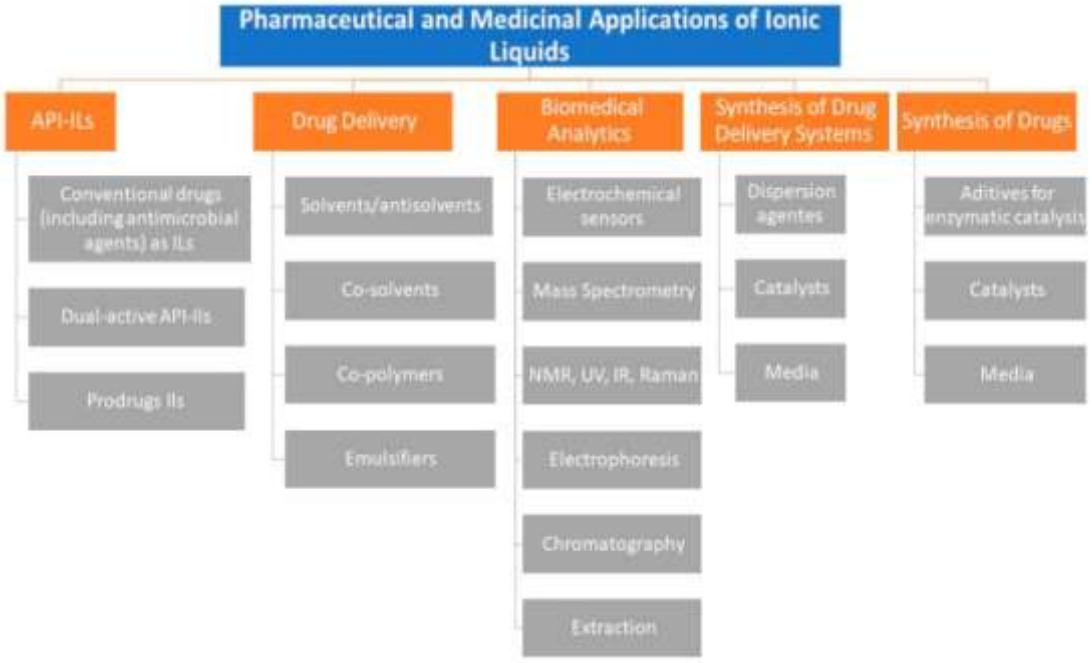
| | | | |
|---|---|---|---|
| Tetraethylammonium, trihexyl(tetradecyl)phosphonium, cetylpyridinium, 1–ethyl–3–methylimidazolium, 3–(2–hydroxyethyl)–1–methylimidazolium, choline, | penicillin hydrolysate, amoxicillin hydrolysate | Escherichia coli, Staphylococcus aureus | [20] |
| 1-butyl-3-methylimidazolium, [2-(4-hydroxyethoxy)ethyl]-3methylimidazolium, 1-(3-hydroxypropyl)-3-methylimidazolium, imidazolium | salicylate | Staphylococcus aureus, Bacillus subtilis. Enterococcus faecalis, Proteus mirabilis, Escherichia coli, Pseudomonas aeruginosa | [21] |
| 3-methyl-1-alkylimidazolium, 3-methy-1-alkyllimidazoliumfuranchalcone hybrid | bromide, tetrafluoroborate, hydroxide | Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus cereus, Streptococcus mutans, Streptococcus agalactiae, Bacillus subtilis | [22] |

**APPLICATIONS**




(Fig. 2)A summary of many pharmaceutiacal and many applications of many IL's (adapted from Egoravaet a) l. [23]

ILs are used in a wide variety of pharmaceutical and medical applications [24 23 25]
Today, ILs are already used in numerous areas of the pharmaceutical industry as solvents in the production of drugs as well as components of drugs or drug delivery systems. [24 23 25] Due to their biological function, ILs are being researched [24]

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their applications in biomedicine [26], and their ability to control microbes [27 28 29]
Furthermore taking into account their toxicity for the environment [30], and cytotoxicity against cancer cell [31 32], with some research looking into the potential for IL biodegradation Figure 1 gives a review of the numerous pharmaceutical and medical uses of ILs.

**MERITS [33]**

- Number of potential solvents - Up to 1018 ionic liquids are conceivable.
- Tunability - Depending on the application, different capabilities and alkyl chain length can be adjusted.
- Vapor pressure: In typical circumstances, there is little to no vapour pressure.
- Non-volatile as a result.
- Flammability: Non-flammable.
- Detachability - It is simple to separate volatile chemicals.
- Stability - Stable across a broad range of temperatures and electrochemical breakdown potentials o high density

**DEMERITS [33]**

- Financial value - Molecular solvents are between 5 and 20 times more expensive.
- Ionic liquids that are entirely pure are quite viscous.
- Vapor pressure - During distillation, solvent separation is hampered by low vapour pressure.
- Synthesis - Usually a time-consuming, expensive, and multi-step process.
- Though environmentally friendly solvents, they are frequently poisonous, non-biodegradable, and unsustainable.
- High levels of hygroscopicity are present in the majority of ionic liquids.
- Corrosiveness - Highly corrosive substances demand particular storage containers.

**IONIC LIQUIDS AND DRUG DELIVERY**

Recently, the application of ILs for medication delivery has been examined [34,35,36-38]. They are typically used in formulations or to change the pharmacokinetic characteristics of drugs, such as their solubility, stability, and/or permeability across biological membranes.

Monocationic ILs are used as carriers to enhance the effectiveness and minimize side effects of antimicrobial medications. They typically serve to permeate bacterial membranes. Synergistic permeation enhancers have been used effectively in a number of cases, including those involving 1-octyl-3-methylimidazolium-based ILs, choline and terpene-bioinspired ILs, and amine-based ILs, among others [39].

However, there is little information that has been published about the use of dicationic ILs and their advantages in drug delivery. On the basis of this idea and using IL chemistry as basis, dual-active API-ILs have also been created. In this aspect, ILs serve as the counterions to active antimicrobial medicines, which can function as anion or cation moieties. The hydrophilicity/hydrophobicity of the counter ion, which can be employed as a modifying factor to tune the solubility and activity against various bacterial strains, is what causes API-ILs to have a dual impact [40,41].

A number of antibiotics, including ampicillin, ciprofloxacin, norfloxacin, nalidixic acid, penicillin G, amoxicillin, colistin, and antimicrobial peptides, have had their performance enhanced by the API-IL approach. The effectiveness of the antibiotic was increased by the addition of polymyxin B to 1-butyl-3-methylimidazolium chloride and 1-butyl-3-methylimidazolium tetrafluoroborate [42].

The combination of ampicillin and quaternary ammonium ILs has received the greatest research [43]. Additionally, a number of organic cations, including imidazolium, pyridinium, and choline, have been effectively combined with ampicillin [44]. Because Gram-positive bacteria do not have an outer membrane, these API-ILs are typically more potent against them and can lower the ampicillin concentration needed to achieve the desired antimicrobial effects.

It is difficult to develop medication delivery systems by nanoencapsulating antimicrobial pharmaceuticals using nano-based ILs methods. The characterization or coating of silver, gold, and zinc oxide nanoparticles has so far been accomplished using ILs (NPs). When it comes to antibacterial activity against different bacteria, this sort of NPs has been shown to be synergistic [45,46-49]. These mixtures possess exceptional chemical, physical, and antibacterial qualities as well as a high surface area to volume ratio [50]. In addition, successful applications of nano-assembled systems, such as those based on phosphonium salts, have been reported [51].

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**Physiochemical Properties Of Ionic Liquids**

1. Conductivity: Greater ionic conductivity in comparison to electrolyte/organic solvent systems. This isinversely associated to viscosity [52].
2. Viscosity: Generally more viscous than usual solvents for molecules. The determination of viscosity byhydrogen and van der Waals forces bonding and cation's alkyl chain length [52].
3. Density: Generally denser than water [52].
4. Melting point: <100°C
5.Solubility: Ionic liquids can act as hydrogen bonding anddonors (cation), acceptors (anion), and such that chemicals can interact with both accepting and donating sites. According to their solubility in water ionic liquids are divided into two categories (water miscible and water immiscible). Examples of Ionic solutions that are water immiscible are butyl-3-methylimidazolium hexafluorophosphate and 1-decyl-3-methylimidazoliumbis(trifluoromethylsulfonyl)imide. Water miscible examples of ionic liquid include 1-Butyl-3-methylimidazolium tetrafluoroborate. Ionic miscibility water's ability to hold liquids depends mainly on the anion present & composition of thecation [53].
6. Thermal stability: Quite thermally stable (some up to 450°C) [52].
7.Chemical stability: In terms of both organic and inorganic compounds, most are stable [54].
8. Electrochemical window: Wide electrochemical window [52].

**FUTURE PROSPECTIVES**

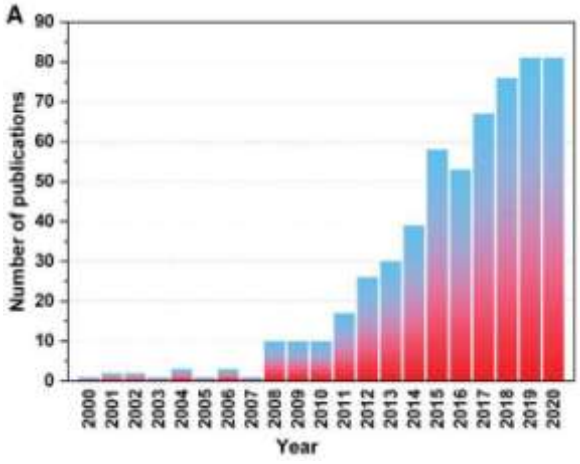
The awareness of and knowledge of how human activity affects the environment is expanding in modern civilization. In this regard, there is growing interest in "green chemistry," which refers to chemical compounds that are thought to be good for the environment. Green solvents are known as ionic liquids based on imidazole molecules. This is significant because interactions between medications with either a general or local use take place most frequently in the aquatic environment. The production of ILs with particular pharmacologic features targeted against bacteria, viruses, and fungi is made possible by the combination of cation and anion.

For a synergistic antibacterial action, it is currently possible to combine b - lactam antibiotics with dimethylimidazolium.

The length of the alkyl chain and the kind of cation affect how harmful ILs (antimicrobial activity) are to the Gram (-) and Gram (+) bacterial strains and fungi that were studied. ILs that have alkyl chains with eight to 18 carbon atoms in them alter the surface charge of bacterial and fungal cell walls. Eventually, they cause metabolic problems and cell death by activating particular gene expression pathways. The example of the quaternary alkylammonium salts provided is particularly clear in terms of the observed impact. ILs are efficient at removing bacterial biofilms, but further research is needed to identify the precise processes by which they function[55].

## II. CONCLUSION

Statistics of published data on biomedical applications of ionic liquid derivatives as antimicrobial agents




(Fig. 3.1) The number of publications related to the bactericidal effect of ionic liquid derivatives by year of publication.

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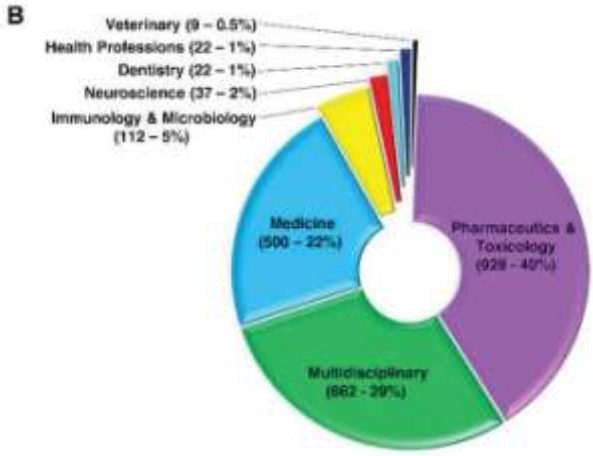


(Fig. 3.2) The number of publications on the biomedical applications of ionic liquid derivatives; the parentheses′ data shows the number of publications and related percentages.

Salts constitute almost half of the medications sold in pharmacies. When compared to solid salts, liquid salts that are at body temperature or room temperature have better solubility, constancy, and adsorbability. [1]

Ionic liquids can therefore be developed and set up to deliver at least two active biological agents at once. For example, procainium salicylate is an ionic liquid that simultaneously gives the body both an analgesic (procaine) and a nonsteroidal anti-inflammatory medication (salicylic acid). [1]

Ionic liquids have been largely neglected during the past ten years because of a lack of skills and understanding through these materials. The development, investment, and commercialization of ionic liquid-based antibacterial compounds are deemed too risky by pharmaceutical corporations. Recent years have seen a boom in interest in the development of antibacterial ionic liquid derivatives as sustainable, effective, and commercially feasible antibacterial agents, thanks to the absence of effective antibiotics against multidrug-resistant bacteria. This is especially true in light of the growing global health hazard posed by antibiotic resistance, which raises morbidity and mortality rates. According to statistics, the number of papers discussing the bactericidal impact of ionic liquids has increased yearly (Fig. 3.1).

In these publications, new ionic liquid-based antibacterial agents are synthesised, surfaces are modified with ionic liquids, common antibiotics are structurally modified with ionic liquids, and their potential use in biomedical research to stop infectious diseases brought on by bacteria is discussed. The proportion of studies on antibacterial activity is low among ionic liquid derivatives used in biomedical applications. However, it is projected that in the upcoming years, the number of publications on the antibacterial impact of ionic liquids will increase due to the urgent need to research and develop alternatives to treat infections caused by multidrugresistant bacteria.

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