Design and development of Conventional and Non-Conventional Antibiotics and their comparative analysis

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In the present scenario, design and development of effective drugs to overcome the therapeutic problems associated with over exploited antibiotics for the treatment of infections is becoming a challenge due to emergence of drug resistant microorganisms. These resistances may result in deactivation of antibiotics, development of adaptation by organisms bypassing the targeted binding sites, change in the mechanism of action and so on. Many strategies have been adopted to interrupt the multiple pathways developed by microorganisms. These include, structural modification of β-lactam antibiotics and β-lactamase inhibitors, combined drug therapy using proportionate mixture of conventional and nonconventional antibiotics. Semi synthetic cephalosporins group of antibiotics act as broad-spectrum antibacterial agents. The enhanced activity of these drugs may be due to availability of higher level of drugs at the target site because all the molecules are having biodegradable ester bonds. Cationic antimicrobial peptides (AMP) are promising alternatives as candidates in future to act against resistant organisms. They offer synergistic effect when used in combination with traditional antibiotics. QSAR modelling based on physicochemical properties of cationic AMPs can serve as useful tool in peptide design and development of suitable AMPs with enhanced activity and diminished toxicity.

Keywords Antibiotics; Cephalosporins; Antimicrobial peptides; Cationic antimicrobial peptides.

1. Introduction

Microorganisms are man’s best friend and worst enemy; though it took several decades to understand their role in human life. Medical treatment of disease was quite difficult before the discovery of penicillin by Alexander Fleming in 1929 which opened a new era of chemotherapeutic agents as antibiotics [1]. The antibiotics available in the pharmaceutical market can be grouped in different categories on the basis of their mode of action, e.g. cell wall synthesis inhibition, protein synthesis inhibition, DNA/RNA synthesis inhibition, folic acid synthesis inhibition etc. as depicted in Table I. The β-lactam antibiotics like penicillin, cephalosporins, vancomycin, etc. are specific inhibitor working against bacterial cell wall (peptidoglycan) synthesis but newer strains of bacteria have β-lactamase activity which destroy most of the β-lactam antibiotics and thus make them resistant to it. The emergence of newly developed microbial strains of antibiotic resistant has become a serious medical problem since last few decades. Exclusive research focused on the ways to solve the problem is going on which include development of new classes of antimicrobial agents and ‘combined drug therapy’, involving both conventional and nonconventional antibiotics. Antimicrobial peptides, individually or in combination with conventional antibiotics, can serve as better alternatives/ substitutes to treat the infection judiciously [2, 3]. Optimisation of structural variation through quantitative structure activity relationship descriptors serves as useful tool to design antimicrobial peptides without compromise with their antimicrobial activity. The best method, proposed for studying the biological activities of AMPs, is to study the synthetic mimetic of AMPs (SMAMPs)
### Table 1 Different mode of activity/action of major antibiotics. [4]

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Source</th>
<th>Mode of action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A) Antifungal antibiotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphotericin B</td>
<td><em>Streptomyces nodosus</em></td>
<td>Membrane function</td>
</tr>
<tr>
<td>Cycloheximide</td>
<td><em>Streptomyces griseus</em></td>
<td>Protein synthesis</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td><em>Penicillium griseofulvum</em></td>
<td>Cell-wall, microtubules</td>
</tr>
<tr>
<td>Nystatin</td>
<td><em>Streptomyces noursei</em></td>
<td>Damages cell-membrane</td>
</tr>
<tr>
<td><strong>B) Antiprotozoan antibiotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fumagilin</td>
<td><em>Aspergillus fumigatus</em></td>
<td>Protein synthesis</td>
</tr>
<tr>
<td><strong>C) Antibacterial antibiotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacitracin</td>
<td><em>Bacillus subtilis</em></td>
<td>Cell-wall synthesis</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td><em>Cephalosporium sp.</em></td>
<td>Cell-wall synthesis</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td><em>Streptomyces venezuelae</em></td>
<td>Protein synthesis</td>
</tr>
<tr>
<td>Cycloserin</td>
<td><em>Streptomyces leavendulae</em></td>
<td>Cell-wall synthesis</td>
</tr>
<tr>
<td>Erythromycin</td>
<td><em>Streptomyces erythraeus</em></td>
<td>Protein synthesis</td>
</tr>
<tr>
<td>Kanamycin</td>
<td><em>Streptomyces kanomycetois</em></td>
<td>Protein synthesis</td>
</tr>
<tr>
<td>Linomycin</td>
<td><em>Streptomyces lincolnhensis</em></td>
<td>Protein synthesis</td>
</tr>
<tr>
<td>Neomycin</td>
<td><em>Streptomyces fradiae</em></td>
<td>Protein synthesis</td>
</tr>
<tr>
<td>Novobiocin</td>
<td><em>Streptomyces sp.</em></td>
<td>DNA synthesis</td>
</tr>
<tr>
<td>Penicillin</td>
<td><em>Penicillium sp.</em></td>
<td>Cell-wall synthesis</td>
</tr>
<tr>
<td>Polymixin</td>
<td><em>Bacillus polymyxa</em></td>
<td>Cell membrane</td>
</tr>
<tr>
<td>Streptomycin</td>
<td><em>Streptomyces griseus</em></td>
<td>Protein synthesis</td>
</tr>
<tr>
<td>Tetracycline</td>
<td><em>Streptomyces aureofaciens</em></td>
<td>Protein synthesis</td>
</tr>
<tr>
<td>Vancomycin</td>
<td><em>Streptomyces orientalis</em></td>
<td>Cell-wall synthesis</td>
</tr>
</tbody>
</table>

### 2. β-Lactam Antibiotics: Cephalosporins

Among the β-lactam antibiotics, cephalosporins are known to be more active than penicillins for the prophylaxis and treatment of bacterial infections caused by susceptible microorganisms. Interactions with cephalosporin side chains occurs in the groove, closed in the free PBP 2a enzyme, binds to the 7-acyl amino side chain, and in another extended groove where it interacts with the 3'-cephem side chain through noncovalent interactions [5]. It is stable to class A penicillinases produced by *S. aureus* and enteric gram-negative microorganisms and is more stable to few class C beta-lactamases of enteric gram-negative microorganisms [6]. Different processing strategies and various modes of bioreactors have been employed for microbial production of cephalosporin C [64,65].

Occurrence of bacterial strains that are resistant to already existing antibiotics such as methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant *E. faecalis* (VRE) has led to the search of new semi-synthetic cephalosporins with better solubility and different mechanism of action. First generation cephalosporins are predominantly effective against gram positive bacteria while successive generations have enhanced activity against the gram negative bacteria (Table II) [7]. Chemical modification of Cephalosporin C allowed production of a series of semisynthetic cephalosporins which can be used as therapeutics to fight against penicillin resistant organisms. These semi-synthetic cephalosporins are classified based on their activity profile, the antibacterial spectrum, mode of action and structure. Each newer generation of cephalosporin has significantly greater gram negative antimicrobial properties than the preceding generations, in most of the cases with decreased activity against gram positive organisms [8].

The first generation cephalosporins, synthesized biochemically using different processing strategies [9]. (Figure1), can permeate the outer membrane of gram-negative bacilli faster than the penicillins. However, they fail to bind well to penicillin binding proteins (PBPs) of the *Enterococci*.  

The second generation cephalosporins (Figure 2) have enhanced activity against gram-negative microorganisms [10-12]. Cefoxitin has an extra methoxy-group that imparts protection against $\beta$-lactamase, but with an added disadvantage that it causes induction of the chromosomal $\beta$-lactamases in several bacterial organisms (which can be counterproductive). Cefuroxime is generally used for respiratory tract and community acquired infections. Cefoxitin (as well as Cefotetan) is well effective against *Bacteroides fragilis*, an enteric anaerobe but not against *Pseudomonas* or *Enterobacter*.

Broad spectrum of antimicrobial activity including gram positive, gram negative, and selected anaerobic species is recorded for third-generation cephalosporins [13] (Figure 3). They show remarkable potency against *Enterobacteriaceae*, including the $\beta$-lactamase-producing strains [1]. The aminothiazolyl and iminomethoxy groups in third generation cephalosporins impart greater stability against the chromosomal class C $\beta$-lactamases with an increased spectrum of activity [14]. A greater potential is shown by these antibiotics in the form of sodium salts. Cefotaxime has an enhanced affinity to penicillin binding proteins (PBP$s$) of gram-negative bacteria and thus it can penetrate faster into bacterial cell as compared to older generation of cephalosporins. Also, cefotaxime is the main intermediary in the synthesis of cefpodoxime proxetil, a third generation oral cephalosporin, introduced recently into medical practice [15, 16].
In hospital born infections, β-lactamase induction or resistant organism selections pose to be an important issue [17]. Third generation cephalosporins vary in their ability to induce β-lactamases, but none of them are as effective inducers as the cephemycins, clavams, or carbapenems. Klebsiella isolates were reported to be resistant to oxy imino cephalosporin and imparted more difficulties to β-lactam antibiotics mediated by extended-spectrum β-lactamases (ESBLs). Mutation in the structural genes of plasmid-mediated TEM, SHV, and OXA β-lactamases and to a lesser extent in the PER and CTX enzymes enhanced their affinity for third generation cephalosporins and monobactams[18] .

The fourth generation cephalosporins (Figure 4) contain 7-amino-thiazolyl groups and a positively charged quaternary nitrogen atom at C-3, resulting in higher activity (compared to the third-generation cephalosporins) against β-lactamase derepressed mutants of P. aeruginosa and other enteric bacteria [19, 20]. It is stable to hydrolysis by the more common chromosomal and plasmid-mediated β-lactamases, and it is quite stable against inducible chromosomally mediated cephalosporinases.

However the efforts are not sufficient enough to get cephalosporins with well balanced broad spectrum activity and improved beta-lactamase stability.

The requirement of present generation is to search new antibiotics specifically active against nosocomial infections of MRSA and Pseudomonas based refractory infection in immunocompromised patients. Although significant work is going on in research sector to synthesize new structurally modified cephalosporins, fifth generation cephalosporins with
required activity are still in pipeline. Drugs which are in immediate attention of FDA are Ceftobiprole, LB10522 and RU-59863 (Figure 5). Ceftobiprole specifically attacks by binding to this penicillin-resistant target [18].

![Ceftobiprole](image1)

![Ceftobiprole medocaril](image2)

![LB10522](image3)

![RU-59863](image4)

Fig. 5 Fifth generation Cephalosporins

Different approaches have been made by several groups of workers to synthesise different generations of antibiotics which mainly involve structural modification of cephalosporin-C or 7- aminoccephalosporanic acid (7-ACA), derived from cephalosporin-C side chain.

In order to fulfil the need of large quantity of semi-synthetic cephalosporin, the key intermediates should be produced in large quantity through very efficient and cheap production routes. Chemical production of the intermediates generates large quantities of wastes and requires expensive and hazardous chemicals and reaction conditions. In order to overcome these problems, enzymes are used to perform the required reactions.

Table 2 Different generation of Cephalosporins [18]

<table>
<thead>
<tr>
<th>Generation</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>First generation Cephalosporins</td>
<td>Cephalothin</td>
</tr>
<tr>
<td></td>
<td>Cephaloridine</td>
</tr>
<tr>
<td></td>
<td>Cephazolin</td>
</tr>
<tr>
<td></td>
<td>Cephradine</td>
</tr>
<tr>
<td></td>
<td>Cefroxadine</td>
</tr>
<tr>
<td>Second generation Cephalosporins</td>
<td>Cephamandole</td>
</tr>
<tr>
<td></td>
<td>Cefuroime</td>
</tr>
<tr>
<td></td>
<td>Ceforanide</td>
</tr>
<tr>
<td></td>
<td>Cefotiam</td>
</tr>
<tr>
<td>Third generation Cephalosporins</td>
<td>Cefotaxime</td>
</tr>
<tr>
<td></td>
<td>Cefuzidime</td>
</tr>
<tr>
<td></td>
<td>Ceftizoxime</td>
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<tr>
<td></td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td></td>
<td>Cefixime</td>
</tr>
<tr>
<td></td>
<td>Cefitutbene</td>
</tr>
<tr>
<td>Fourth generation Cephalosporins</td>
<td>Cefipime</td>
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<td></td>
<td>Cefpirome</td>
</tr>
</tbody>
</table>
Cephalosporin-C can be produced by free and immobilized microbial cells [21] using various cultivation modes of batch (in stirred bioreactors as well as in air lift bioreactor) and continuous strategy (in packed bed bioreactor and continuous stirred tank bioreactor [22-25]. The process being highly aerobic, cephalosporin-C is also produced by immobilized microbial cells utilizing symbiotic mode (in-situ oxygen production) in a packed bed bioreactor [26].

Fig. 6 The structure of Cephalosporin C

Cephalosporin C is converted to 7-ACA by side chain is deamination using D-amino oxidiser, (resulting in a α-keto acid that spontaneously loses carbon dioxide in the presence of hydrogen peroxide to form glutaryl-7-ACA) followed by enzymatic deacylation using cephalosporin acylase which removes a charged aliphatic side chain without damaging the β-lactam nucleus.

Cephalosporins prepared by alteration of the side chains of IInd and IIIrd generation antibiotics are shown to have tremendous scope to combat with the resistant organisms [27].

3. Combined drug therapy: a better alternative

Recent few years have witnessed considerable studies on the use of combination of two or more antibiotics for the treatment of multiple drug resistant bacterial infections. Conventional antibiotics like ciprofloxacin, levofloxacin, gatifloxacin and moxifloxacin were shown to have synergic activity against clinical isolates of P. aeruginosa when tested in combination with ceftazidime or cefepime. Combination of ceftazidime or cefepime and fluoroquinolone was reported to result in vitro synergy in 60–80% of tested P. aeruginosa clinical isolates. [28]. In a recent review by Worthington and Melander (2013), it has been pointed out that ‘cocktails’ of drugs in the form of antibiotic - antibiotic or antibiotic - adjuvant combinations [29] can reduce the chance of resistance development by the organisms much more than structurally modified new antibiotics alone. The combined drug action may mediate either in a traditional manner through target resistance mechanism as in case of clavulanic acid or indirectly by interfering with bacterial signaling pathways. Thus, antibiotic-adjuvant combination can serve as an alternative approach to treat infections caused by resistant organisms. The enhancement of antibiotic activity or the reversal of antibiotic resistance by non-conventional antibiotics affords the classification of these compounds as modifiers of antibiotic activity [30].

4. Non Conventional Antibiotics (Antimicrobial peptide)

Antimicrobial peptides (AMP) are short peptides of length less than 50 amino acids that are a part of the innate defence mechanism of all the classes of organisms from prokaryotes to eukaryotes. Due to the increase in the bacterial resistance against the conventional antibiotics, the antimicrobial peptides are taken into consideration as an alternative for the conventional antibiotics.

4.1. Classification of Antimicrobial peptides

Antimicrobial peptides can be classified into anionic antimicrobial peptides (AAMP) and cationic antimicrobial peptides (CAMP) on the basis of charge [31, 32]. The AAMPs are negatively charged with a charge ranging from -1 to -7 [31]. The AAMPs are abundant in negatively charged amino acids which give them a net negative charge. The mechanism of action of AAMPs for the killing of microorganisms has not been well established yet. Maximin H5 from amphibians and Dermcidin from humans are some examples of AAMP [32].
The CAMPs are positively charged with charges ranging from +2 to +11 [31]. The abundance of the positively charged amino acids like lysine, histidine and arginine are responsible for the net positive charge of these peptides. These positively charged peptides have a strong electrostatic attraction towards the negatively charged cell membrane surface of the bacterial membranes. The eukaryotic cell membrane is neutral charged on its surface [33]; hence these have weak attraction towards it. Due to this characteristic the CAMP get attracted only towards the prokaryotic cell membrane and not towards the eukaryotic cell membrane. The higher percentage of hydrophobic residues of CAMPs also helps them to penetrate the cell membrane. Therefore the chances of CAMP being harmful to the host are minimized. Hence, the medical practitioners and the scientists are working to develop antimicrobial peptides as an alternative for the conventional antibiotics to combat the problem of drug resistant bacteria. The characteristics of Bioactive Cationic Antimicrobial peptides have been described in Table III.

CAMPs have different structures and accordingly classified as α-helical cationic antimicrobial peptide, β-sheet cationic antimicrobial peptide, linear cationic antimicrobial peptide and loop structure cationic antimicrobial peptide. The first two are found commonly in nature [34]. The α-helical cationic antimicrobial peptides do not possess any disulphide bridges as they lack cysteine. LL-37, cecropins, magainins are some examples of α-helical CAMP. The β-sheet CAMPs possess two to five disulphide bridges. Human α and β defensins, plectasin, protegrins are some examples of β-sheet CAMP. The linear CAMPs are rich in glycine, proline, tryptophan, arginine and/or histidine. Indolicidin is one of the examples of linear CAMP. The loop structure CAMPs possess one disulphide bridge. Bactenecin and thanatin are some examples of loop structure CAMP. The following PDB files were downloaded from RCSB database. [35]

4.2. Mode of action of CAMP

Bacterial membranes are abundant in negatively charged lipids having phospholipid head groups, for example, phosphatidylglycerol, cardiolipin and phosphatidylserine, whereas the mammalian membranes are abundant in zwitterionic phospholipids, like phosphatidylethanolamine, phosphatidyleholine and sphingomyelin [36]. Hence, the positively charged CAMP show a high electrostatic attraction for the negatively charged bacterial membrane and a weak electrostatic attraction for mammalian membrane which is neutral charged.

The CAMP kill the bacterial cells by either disrupting their cell membrane or by targeting the intracellular targets and inhibiting the essential processes required for the survival of microorganisms. The net negative charge, hydrophobic nature and the amphiphillic nature of the CAMP are responsible for the mode of action of the CAMP against bacteria [37]. Initially the CAMPs are attracted towards the bacterial membrane because of the electrostatic attraction. Because
of the attraction the antimicrobial peptides start accumulating on the bacterial membrane surface. After reaching a
threshold concentration of accumulation, the antimicrobial peptides start penetrating inside the bacterial membrane
where they attack the intracellular targets.

4.2.1. Penetration of CAMPs in the cell membrane
There are three mechanisms by which the CAMPs penetrate the cell membrane - Barrel-Stave Mechanism Toroid
Pore or Wormhole Mechanism and Carpet Mechanism [32, 36, and 38].

4.2.1.1. The Barrel-Stave Mechanism:
The peptides are positioned around an aqueous pore in a barrel like ring. The hydrophobic surfaces of the CAMPs face
towards the outside of the pore where they come in contact with the acyl chains of the membrane. The hydrophilic
surfaces form the inner lining of the pore. The positively charged amino acids are positioned near the phospholipid head
groups. The peptides undergo a conformational phase transition when they bind to the surface of bacterial cell
membrane. In this process the polar head groups of the membrane move aside thus causing membrane thinning and the
hydrophobic surface of the CAMP penetrates here. As the number of bound peptides reach a threshold concentration
then the CAMPs aggregate. This aggregation causes pore to expand and the CAMPs traverse across the membrane.

4.2.1.2. Toroid Pore or Wormhole Mechanism:
In this model the CAMPs intercalate with the bacterial cell membrane. The CAMPs acquire α- helical configuration.
The polar region of the CAMPs and the polar head group of the lipids in the membrane interact with each other. The
CAMPs align themselves perpendicular to the membrane. The hydrophobic regions of the CAMPs interact with the
hydrophobic tails of the lipids in membrane. Thus a transient toroidal pore complex is formed. Some peptides are
transferred to the cytoplasm when these pores disintegrate.

4.2.1.3. The Carpet Mechanism:
The CAMPs accumulate on the bacterial membrane surface, like a carpet, in high density. The CAMPs align parallel to
the membrane surface. When a threshold concentration is reached then the membrane integrity is lost due to
unfavourable energetic. This concentrated layer of CAMPs on the surface causes destabilization of phospholipid
packaging and thus leads to membrane disruption.

4.2.2. Mechanism of Cell death
The cationic antimicrobial peptides follow various mechanisms for causing cell death. The CAMPs attach with the cell
membrane and cause membrane dysfunction. These CAMPs can enter inside the cell and they can inhibit the synthesis
of extracellular biopolymers or they can inhibit the intracellular functions.

The cell membranes play a very crucial role in many cellular functions, e.g. maintenance of gradients, cellular
energetic, selective permeability, etc. Membrane dysfunction can interfere with some of these crucial functions and thus
kill the bacteria either directly or indirectly. The membrane disruption can cause leakage of ions or metabolites,
depolarization of membrane, etc., which can lead to the cell death. Antimicrobial peptides interact independently with
the outer and inner membrane of gram- negative bacteria. When gram- positive cells are exposed to antimicrobial
peptides, then immediate increase in water and ion flow causes swelling and osmotic dysregulation. Thus, the cell
membrane dysfunction can cause a major role in leading to cell death due to the action of CAMP.

The CAMPs can also inhibit the biosynthesis of some extracellular macromolecules like peptidoglycan, chitin etc.
This is possible because the synthesis of these extracellular macromolecules is dependent on the cell membrane
integrity. Thus, loss of membrane integrity inhibits their synthesis, leading ultimately to cell death.

There are some cases where the cells survive for some time after membrane permeabilization and then cell death
occurs so in these cases it can be concluded that the cell death occurred not by membrane dysfunction but some other
reason. These CAMPs kill the microorganisms by disrupting some intracellular functions like inhibition of DNA, RNA
or peptide synthesis, etc.

4.3. Therapeutic potential of antimicrobial peptide
Naturally occurring AMPs have enough scope to act as antibacterial agent alone or in combination with traditional
antibiotics. Therapeutic potential of antimicrobial peptides have been studied by different groups of workers. Several
cationic antimicrobial peptides are being tested for their efficiency as as antimicrobial agents and found to possess
broad spectrum of activity. Peptides from the seed and pod of Pisum sativum L. were found to be active against bacteria
[39]. Fresh aqueous extract of garlic showed inhibition of growth for some Salmonella serovars [40]. BEP-1 isolated
from Bullacta exarata showed activity against human pathogen strains such as *Staphylococcus epidermis*, *E. coli* and Methecillin-Resistant *Staphylococcus aureus* [41].

The microorganisms have less probability to develop resistance against these CAMPs peptides on excessive use. This is because the antimicrobial peptides are short peptides which interact with the bacterial membrane. To develop resistance a large part of the bacterial membrane needs to be modified, which is a very energy consuming process [42]. Generally the antimicrobial peptides are found non toxic for the eukaryotes as they are specific to get attracted towards the prokaryote.

Several antimicrobial peptide drugs are being tested; some are in the early phase of development (phase I, II and preclinical) while some are in the late clinical stage (phase III and advance). Only few of them have crossed all these barriers to reach the market [34]. There are some problems in the path of developing antimicrobial peptides as drugs particularly because these antimicrobial peptides are susceptible to proteases, change in pH, etc. [43, 48]. Also, the cost of production of antimicrobial peptides is comparatively higher than conventional antibiotics [38, 43].

Studies are being carried out to tackle all the aforementioned problems through different approaches. The AMPs are mostly found in the L- configuration in nature, which are prone to be degraded by the proteases and hence rendered harmless for the pathogens. To overcome this challenge, the antimicrobial peptides are synthesized in their D-form, which is unnatural and the proteases cannot degrade them as it is not their substrate for action [43]. Some properties of an antimicrobial peptide D1 (K13) were changed, which lead to improvement in its action against gram negative bacteria [44]. Several efforts are being carried out to develop antimicrobial peptides as drugs which are less toxic with no compromise with their antimicrobial activity. Work is being carried out to design antimicrobial peptides to serve as a substitute of conventional antibiotics. The best method, proposed for studying the biological activities of AMPs is to study the synthetic mimetic of AMPs (SMAMPs) [45]. QSAR modelling based on physicochemical properties of cationic AMPs can serve as useful tool in peptide design [62, 63] and development of suitable AMPs with enhanced activity and diminished toxicity.

Table 3 Characteristics of Bioactive Cationic Antimicrobial peptides [49]

<table>
<thead>
<tr>
<th>S.no.</th>
<th>Name of antimicrobial peptides</th>
<th>Source</th>
<th>Sequence</th>
<th>Hydropathicity</th>
<th>Charge</th>
<th>Activity</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Aurein 2.1</td>
<td><em>Litoria aurea</em> or <em>Litoria raniformis</em></td>
<td>GLLDIVKVVVG AFGSL</td>
<td>56%</td>
<td>2</td>
<td>Gram+ &amp; Gram-, Fungi, Cancer cells</td>
<td>[50]</td>
</tr>
<tr>
<td>2</td>
<td>Thanatin</td>
<td><em>Podisus maculiventris</em></td>
<td>GSKKPVPPIYCN RRTGKCQRM</td>
<td>28%</td>
<td>6</td>
<td>Gram+ &amp; Gram-, Fungi</td>
<td>[51]</td>
</tr>
<tr>
<td>3</td>
<td>Cecropin A</td>
<td>peptide hybrid</td>
<td>KWKLFKKIKFL IHSAKKF</td>
<td>47%</td>
<td>7</td>
<td>Virus, Cancer cells</td>
<td>[52]</td>
</tr>
<tr>
<td>4</td>
<td>Plantaricin A</td>
<td><em>Lactobacillus plantarum</em></td>
<td>KSSAYSLQMGA TAIIQKVKLF KWGW</td>
<td>42%</td>
<td>6</td>
<td>Gram+ &amp; Gram-, Fungi</td>
<td>[53]</td>
</tr>
<tr>
<td>5</td>
<td>Dermaseptin-S1</td>
<td><em>Phyllomedusa sauvagii</em></td>
<td>ALWKTLKKL GTMALHAGKA ALGAAADTISQ GTQ</td>
<td>50%</td>
<td>3</td>
<td>Gram+ &amp; Gram-, Virus, Fungi, Parasites, Sperms, HIV</td>
<td>[54]</td>
</tr>
<tr>
<td>6</td>
<td>Pleurocidin</td>
<td>Winter flounder, <em>Pleurone ctes americanus</em></td>
<td>GWGSFFKKAAD VGLKHVGKAALT HYL</td>
<td>44%</td>
<td>4</td>
<td>Gram+ &amp; Gram-</td>
<td>[55]</td>
</tr>
<tr>
<td>7</td>
<td>Cycloviolacin O2</td>
<td><em>Viola odorata</em></td>
<td>GIPCGESCWVPI CISSAIGCSCKSK VCYRN</td>
<td>46%</td>
<td>2</td>
<td>Gram-, Parasites, Cancer cells</td>
<td>[56]</td>
</tr>
<tr>
<td>8</td>
<td>VrD1</td>
<td>seeds, <em>Vigna radiata</em></td>
<td>RTCMKKEGWG KCLIDTTCAHSC KNRGYIGGNCK GMTRTCYCLVN C</td>
<td>39%</td>
<td>6</td>
<td>Fungi, Insects</td>
<td>[57]</td>
</tr>
<tr>
<td>9</td>
<td>Nisin Z</td>
<td><em>Lactococcus lactis</em></td>
<td>ITISLCTPGC KT GALMGCNMMK ATCNCSIHVS</td>
<td>44%</td>
<td>3</td>
<td>Gram+</td>
<td>[58]</td>
</tr>
</tbody>
</table>
The antimicrobial peptides are considered as an alternative for the conventional antibiotics. Comparative study of some of the characteristics of the conventional antibiotics and the cationic antimicrobial peptides is presented in the Table IV.

### Table 4: Comparative studies of Conventional antibiotics and Antimicrobial peptides (Non-conventional)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cationic Antimicrobial peptides</th>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biosynthesis</td>
<td>These are coded by genes and synthesized by ribosomes.</td>
<td>These are synthesized in the idiophase by enzymatic action.</td>
</tr>
<tr>
<td>Characteristics</td>
<td>Molecular weight more than 1 kDa. Cationic antimicrobial peptides are amphiphilic, hydrophobic peptides with length less than 50 amino acids.</td>
<td>Molecular weight less than 1 kDa. Antibiotics are the inert products of secondary metabolites that are non toxic to the mother microorganism but toxic to others.</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>The positively charged cationic antimicrobial peptides are attracted towards the negatively charged bacterial membrane by electrostatic attraction. They cause cell death by causing cell membrane dysfunction or inhibition of the some extracellular polymer synthesis or by inhibiting some crucial intracellular functions like DNA, RNA &amp; protein synthesis.[34, 36, 38]</td>
<td>Impairing cell wall synthesis, inhibiting mucopolysaccharides synthesis in cell wall leading to cell lysis and cell death, bind to 30s subunit of ribosome hence inhibiting protein synthesis, causing disruption in cell wall and leakage of cell content by binding to negative charges and thus displacing the cations that bind membrane phospholipids together, inhibiting DNA synthesis and causing cell death, inhibition of synthesis of folic acid intermediates and thus impairing synthesis of nucleotides.[8, 18]</td>
</tr>
<tr>
<td>Application</td>
<td>These can be used as therapeutics, as probiotics, for treatment of wound healing, etc. [43, 60, 61]</td>
<td>Used as therapeutics for the treatment of infections caused by the pathogenic microorganisms.</td>
</tr>
<tr>
<td>Possibility of development of antimicrobial resistance due to over use</td>
<td>Very less</td>
<td>Very high</td>
</tr>
<tr>
<td>Precursor needed</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

#### 5. Conclusion

In general, the application of traditional antibiotics to combat the resistant microorganisms has been unsuccessful. The discovery, development and design of non-traditional antibiotics (antimicrobial peptides) are very much needed for medical treatment of infection/disease caused by resistant microorganisms. This work has highlighted the tremendous scope of developing highly active, stable, nontoxic non-conventional antibiotics with increased potency against a wide range of resistant microorganisms. Although the progress is in preliminary stage but significance of the work is enormous.

### References


