The Remarkable Cationic Peptides: A Boon to Pharmaceutical Sciences?

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ABSTRACT - In this opinion article, the authors discuss a number of interesting, beneficial properties of naturally occurring and synthetic cationic antimicrobial peptides (AMPs) with the prospective aim of bringing these compounds into therapeutic use to avoid antibiotic resistance and utilize their numerous properties. The structural diversity and the conformational freedom of these compounds adversely affects their mechanistic elucidation. Our molecular level mechanistic exploration of these peptides has shown their ion carriage properties and systematically explains their antibiotic activity through disruption of bacterial cell homeostasis and inhibition of 14-α demethylase enzyme. We have also shown self-assemble in AMPs in different nanoparticulate and tubular forms. Some AMPs possess cell penetration capability and their co-administration with drug enhances antibacterial activity through a non-disruptive mechanism. The anti-HIV activity of AMPs has been explained based on their non-covalent, non-base-pair base-pair type interactions with HIV viral ssRNA template. Design of peptidomimetic compounds with enhanced druggability based on our mechanistic explorations will definitely lead to better non-toxic drugs with antibacterial, anti-HIV activity and may contribute towards development of efficient drug delivery systems.

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INTRODUCTION

Antimicrobial peptides (AMPs) are small peptides upto 50 amino acids in length with broad spectrum antimicrobial activity against bacteria, yeasts, fungi, viruses (1). These are naturally occurring peptides produced by all multicellular organisms to protect themselves against pathogens. Some data of flora and fauna produced such AMPs is collected in Table 1 (2-30) which is by no means exhaustive (31). The obvious therapeutic usage of these peptides is in the form of antibiotics. But, the advent of penicillin family and later many semi-synthetic and synthetic antibiotics masked the growth of AMPs as antibiotics. Nevertheless, AMPs being linked to an organism’s defense mechanism play an important role in immune homeostasis (32). Ever increasing cases of antibiotic resistance and immunodeficiency diseases in humans have once again rejuvenated interest in AMPs (33). Despite being revisited a number of times, AMPs have not taken over drug market due to their subtle barriers in pharmacodynamic properties like high molecular weight, slow absorption, proteolysis before reaching target etc. (34). Structural tuning of AMPs for the therapeutic usage of mankind requires extensive knowledge of structure-function correlation and mechanistic aspects.

STRUCTURAL ASPECTS OF AMPs

Several AMPs have been isolated, characterized and synthesized. Typically AMPs are cationic containing more often basic and hydrophobic amino acids that align on opposing faces facilitating their water solubility. Depending upon the length which is typically below 50 amino acid residues these peptides may possess α-helical, β-sheet type or more complicated secondary structure (35). Examples of modelled structures for some of these peptides based largely on solution NMR data are given in Fig. 1. However, they may adopt variable structure at lipid interface (36-38) which allows them to penetrate through cell membrane. Wimley (39) has proposed an interfacial activity model based on interaction of AMPs with lipid membrane. Many AMPs possess disulfide linkages that stabilize their secondary structure (40). This structural diversity does not correlate with their antimicrobial activity. In fact few plausible mechanistic explanations have been put forward for their antimicrobial activity which are discussed in the following section.

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| Table 1. Naturally occurring antimicrobial peptides |
|----------------|-----------------|----------------|-----------------|-----------------|----------------|
| AMP            | Source                  | Antimicrobial activity | Other properties | Gram nature | Ref.  |
|                |                          | Target species          |                  |                |      |
| Aurein 1.2     | Southern bell frog, Litoria raniformis | *C. albicans*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, *Candida tropicalis* (MICs: 16–128 µg/ml), *Candida kefyr* (MIC: 32–256 µg/ml) | Antifungal, Anticancer |                | 2,3  |
| Tigerinin 1    | Indian bullfrog, Rana tigrina | *Saccharomyces cerevisiae* (MIC: 80 µg/ml), *B. subtilis* (MIC = 30 µg/ml), *E. coli* (MIC = 40 µg/ml) | Antibacterial, Antifungal | Gram+ve, Gram-ve | 4    |
| BMAP-27        | Cow, Bos taurus          | *C. albicans*, *C. neoformans* (MICs: 4–16 µM) | Antifungal |                | 5    |
| RTD-1          | Rhesus macaque, Macaca mulatta | *Candida albicans* (MICs: 1µg/ml) | Antifungal | | 6    |
| Hepcidin-20    | Human (liver), H. sapiens | *Aspergillus niger* (spores), *A. fumigatus* (spores) (MIC: complete inhibition at 20-40 µM) | Antibacterial, Antifungal | Gram+ve, Gram-ve | 7,8  |
| Tachyplesin-2  | Southeast Asian horseshoe crab, Tachypleus tridentatus | *Candida albicans* M9 (MIC: 3.1µg/ml) | Antibacterial, Antifungal | Gram+ve, Gram-ve | 9,10 |
| Polyphemusin-1 | American horseshoe crab, Limulus polyphemus | *C. albicans* (MIC: 1.26 µM) | Antibacterial, Antifungal | Gram+ve, Gram-ve | 10   |
| Protegrin-1    | Sus scrofa               | *C. albicans* In vitro (MIC 3.0–60.0 µg/ml) | Antifungal, Antibacterial | | 11   |
| Penetratin     | Fruit fly, Drosophila melanogaster | *C. albicans* (MIC: 100 µM; 95% growth inhibition at 50 µM) | Antifungal | | 12   |
| Vespid chemotactic peptide-5g | Vespine wasp (venom), Vespa magnifica | *C. albicans* (MIC: 12.5 µg/ml) | Antibacterial, Antifungal | Gram+ve, Gram-ve | 13   |
| Ascaphin-8     | American coastal frog, Ascaphus truei | *C. albicans* (MICs: 12–25 µM) | Antibacterial, Antifungal | Gram+ve, Gram-ve | 14   |
| Latarcin 3a | Spider, *Lachesana tarabaevi* |  *P. pastoris, S. cerevisiae* (MIC: 20 µM) | Antibacterial, Antifungal | 15 |
| Gomesin | Tarantula spider *Acanthoscurria gomesiana* |  *Alternaria brassicola, Aspergillus fumigatus, C. albicans, C. tropicalis, Cryptococcus neoformans, Fusarium culmorum, Fusarium oxysporum, Nectria haematococca, Neurospora crassa, S. cerevisiae, Tricoderma viridae, Trichophyton mentagrophytes* (MICs: 0.15–6.25 µM) *Beauveria bassiana, C. glabrata* (MICs: 12.5–25 µM) | Antibacterial, Antifungal, Antiparasitic | 16 |
| Jelleine-I | Honeybee (royal jelly), *Apis mellifera* |  *Candida albicans* (MIC: 2.5 µg/ml) | Antibacterial, Antifungal | 17 |
| Decoralin | Solitary eumenine wasp, *Oreumenes decoratus* (poison) |  *Candida albicans* (MIC: 40 µM), *S.saprophyticus* (MIC = 40 µM), *B.thuringiensis* (MIC = 40 µM) | Antibacterial, Antifungal | 18 |
| Hylin-a1 | Spotted tree frog *Hypsiboas albopunctatus* |  *S.aureus ATCC 25926* (MIC=8 µM), *E.faecalis ATCC 29212* (MIC=16 µM), *B.subtilis ATCC 19659* (MIC=8 µM) *C.albicans ATCC 90028* (MIC=16.7 µM), *C.krusei ATCC 6258* (MIC=16.7 µM), *C.parapsilosis ATCC 22019* (MIC=67 µM), *C.neoformans ATCC 90012* (MIC=33.5 µM) | Antibacterial, Antifungal | 19 |
| Ascalin | Shallot *Allium cepa var. aggregatum* |  *B.cinerea, HIV-1 reverse transcriptase* (IC50 = 10 µM) | Antifungal, Antiviral | 20 |
| Sesquin | Cowpea *Vigna unguiculata subsp. sesquipedalis* |  *Botrytis cinerea* (IC50 = 2.5 µM), *Fusarium oxysporum* (IC50 = 1.4 µM), *Mycosphaerella arachidicola* (IC50 = 0.15 µM) *Proteus vulgaris, Mycobacterium phlei, Bacillus megaterium, B. subtilis, HIV-1 reverse transcriptase* | Antibacterial, Antifungal, Antiviral | 21 |
Table 1. Continued…

| Compound       | Source                  | Antimicrobial Activity                          | References |
|----------------|-------------------------|-------------------------------------------------|------------|
| Rondonin       | Spider, Acanthoscurria rondoniae | Trichosporon sp IOC 4569 (MIC = 1.1 µM), Candida albicans MDM8 (MIC = 16.75 µM), Candida krusei IOC 4559 (MIC = 16.75 µM), Candida glabrata IOC 4565 (MIC = 8.37 µM), Candida albicans IOC 4558 (MIC = 8.37 µM), Candida parapsilosis | 22         |
| OdG1           | Yunnan frog, Odorrana grahami | Escherichia Coli (MIC = 4.68 µg/ml), Staphylococcus aureus (MIC = 9.37 µg/ml), Bacillus subtilis (MIC = 37.5 µg/ml), Candida albicans (MIC = 1.10 µg/ml) | 23         |
| Alpha-MSH      | Human, Homo sapiens     | Staphylococcus aureus, Candida albicans         | 24         |
| Mastoparan-S   | Giant African praying mantis, Sphodromantis viridis | Escherichia coli (MIC = 28.3 µg/ml), Klebsiella pneumoniae (MIC = 26.7 µg/ml), Pseudomonas aeruginosa (MIC = 24.2 µg/ml), Bacillus subtilis (MIC = 17.6 µg/ml), Leuconostoc mesenteroides (MIC = 19.8 µg/ml), Bacillus cereus (MIC = 15.1 µg/ml), Aspergillus niger (MIC = 24.6 µg/ml), Aspergillus fumigates (MIC = 19.3 µg/ml), Candida albicans (MIC = 20.4 µg/ml) | 25         |
| Pantinin-1     | Emperor scorpion, Pandinus imperator | S. aureus(MIC=8 µM), B. magaterium(MIC=32µM), M. luteus(MIC=32µM), vancomycin-resistant Enterococci (MIC=14 µM), E. cloacae(MIC=76µM), S. enterica(MIC=72µM), C. tropicalis(MIC=16µM) | 26         |
| Chitinase      | Streptomyces venezuelae, Streptomyces violaceus | Aspergillus niger, Alternaria alternata, H. sativum | 27         |
| Ranacyclin-E   | Edible frog, Rana esculenta | S. lentus (MIC = 5 µM), M. luteus (MIC = 5 µM), C. tropicalis (MIC = 7.4 µM), C. guillermondii (MIC = 3.4 µM) | 28         |
| Maximin H3     | Giant fire-bellied toad, Bombina maxima | Escherichia coli ATCC25922 (MIC = 20 µg/ml), Staphylococcus aureus ATCC2592 (MIC = 10 µg/ml), Bacillus pyocyaneus CMCCB1010 (MIC = 20 µg/ml), Candida albicans ATCC2002 (MIC = 5 µg/ml) | 29         |
Table 1. Continued…

| Gymnin | Soap tree | *Fusarium oxysporum* (IC50 = 2 µM), *Mycosphaerella arachidicola* (IC50 = 10 µM), *HIV-1 reverse transcriptase* | Antifungal, Antiviral | 30 |
|---|---|---|---|---|

**Figure 1a.** Model structures for some antimicrobial peptides.

**Figure 1b.** Model structures for some antimicrobial peptides.
MECHANISTIC ASPECTS OF AMPs

It is believed that being cationic in nature they interact with the microbial cell wall weakening it to allow seepage of extracellular ions resulting in bloating and eventual death of microbe (c.f. Fig. 2). In the last five years there have been continued efforts to understand and utilize the bacterial membrane disruptive ability of AMPS (41). Sharma et al (42) have described the formation of AMP-lined ion channel which modulate the membrane potential. An interesting computational investigation utilizing molecular dynamics simulation of pore formation has recently been reported (43). A flora derived AMP Snakin-2 was recently studied for its broad spectrum antimicrobial activity and its interaction with cell membrane was investigated by microscopy (44). Lee et al (41) have summarized the usage of biophysical techniques to probe interactions between AMPs and cell membrane.

Our lab has explored mechanistic aspects of properties of these AMPs at the molecular level. We have shown ion carriage characteristics of cyclic counterparts of these peptides (c.f. Fig. 3) (45). For the antifungal peptides another mode of action may be proposed based on the interaction of azole antifungals with 14α-demethylase enzyme active site (c.f. Fig. 4). Since, the antifungal peptides also possess ion affinity they may also interact with heme Fe required for 14α-demethylase activity thus inhibiting the formation of ergosterol an essential component of microbial cell wall. Complete mechanism of AMPs destroying the bacterial or fungal cell is still not known at the molecular level and research along these lines is currently being pursued in our lab. In our opinion the non membrane permeabilizing AMPs (46) may follow a mechanism utilizing ion interaction.

![Figure 2](image.png)

**Figure 2.** Interaction of cationic AMPs with microbial cell wall.
**Figure 3.** Ion carriage characteristics of AMPs.

**Figure 4.** Inhibition of 14-alpha demethylase enzyme by AMPs.
Figure 5. Different self aggregated forms of synthetic AMPs.
OTHER IMPORTANT PROPERTIES OF AMPs

Self assemblage
Some AMPs have the ability to self assemble in different forms either in presence of counterions or in absence of counterions (47). The self assembled forms are highly significant in different ways, for example, in drug delivery systems, as structural materials for different body implants and also in the bottom-up approach to understanding evolution of mankind (48). Different self assembled forms of some peptides are shown in Fig. 5. We have shown tubular structure formation by a completely hydrophobic cyclic peptide [Ala]₁₂ (49, Fig. 5). Cyclic peptide [WR]₄ and [WR]₅ form nanoparticulates upto 50 nm in dimension (50, Fig. 5) which have been captured by TEM images and used to enhance delivery of small anticancer agents. A good hydrophilic lipophilic balance (HLB) is needed for nanoparticulates suitable for drug delivery. The same conclusion has been drawn by another recent study (51) to explain antimicrobial property of these peptides. Some AMPs are under pre-clinical studies for cancer treatment (52).

The magnitude of importance of understanding mechanistic issues of AMPs can only be glimpsed by noticing that cancer cells have recently been shown to develop resistance to chemotherapeutic agents due to the presence of membrane associated multi drug resistant proteins such as P-glycoprotein (53).

Cell penetration capability
Cationic peptides have shown rapid cellular uptake. Researchers have made efforts to utilize this property by conjugating them with nuclear targeted drugs to enhance the cellular uptake of the drug. Covalent linkage is not always a necessity as even co-administration of a cell penetrating peptide (CPP) has shown increased efficacy of anticancer agents (54). Some work along these lines has been done in our lab to show the drug delivery properties of these peptides at molecular level utilizing computational techniques (55). A recent review article (56) discusses covalently linked different conjugates of AMPs for target selectivity or enhanced therapeutic usage. Many pre-clinical and clinical trials are being performed to evaluate the performance of CPPs in drug delivery. Bolhassani et al (57) have discussed the in vitro and in vivo delivery efficiencies of CPPs. CPPs are the non-membrane permeabilizing category of AMPs which translocate through the membrane without disrupting its integrity (58).
Tashima (59) has recently discussed the non-invasive intracellular substance delivery (including macromolecules which are otherwise impermeable) by CPPs.

**Anti HIV activity**

Recent rise in HIV patients has compelled researchers to revisit AMPs for two important reasons: to overcome ever-increasing cases of antibiotic resistance and to overcome the risk of internal fungal infection in HIV patients due to their reduced immunity. It is fascinating to understand how nature has devised these systems to protect flora and fauna from microbial activity. Apart from antimicrobial activity recent studies have shown anti HIV activity of these peptides (60). It is not clear from the literature whether the peptides themselves show anti HIV activity or simply enhance the delivery of anti HIV agents.

Recent computer aided modelling and docking studies from our lab have shown interactions between AMPs and HIV ssRNA primer binding site through interactions other than base pair-base pair type (c.f. Fig. 6). Our studies have shown HIV inhibitory capability of these peptides (61) that can be exploited to design a non-toxic drug with anti HIV and antimicrobial activity.

The question now clearly is that with many interesting and pharmacologically important properties at hand, AMPs to date have not been able to capture the drug market though the researchers have visited and revisited these systems a number of times in search of safe pharmaceuticals. We must therefore put in our best efforts to overcome pharmacodynamic and related ADME issues by design of peptidomimetic compounds. To be able to design peptidomimetic compounds complete structure-function elucidation along with mechanistic details are required. Thimmegowda and Yeldur (62) have correlated the structure function of arginine-rich proteins with their biological significance. In recent years, we have designed peptidomimetic compounds with complete or partial artificial backbone for different pharmaceutical applications (61,63-66). We hope that synthetic organic chemists and pharmaceutical scientists shall come together to synthesize and test these and similar compounds for their ADME properties and prospective druggability features.

Some recent synthetic efforts in this direction are summarized here. Molchanova et al (67) describe α-peptoids, β-peptoids and hybrid peptidomimetic compounds for their antibacterial activity and enhanced stability in body. Cheap synthesis on large scale and bioavailabity have been the biggest hurdle in development of these compounds as commercial drugs. Sgolastra et al have described their efforts towards building synthetic mimics of AMPs (68) using unique molecular scaffolds and guanidinium-rich side chains.

However, much remains to be done at the molecular level for significant advancement in the area of AMPs and their druggable future.

![Figure 6. Single stranded viral RNA template inhibition by antimicrobial peptide through interactions other than base pair-base pair type.](image)
FUTURE DIRECTIVES

This article reiterates the multiple beneficial properties of naturally occurring antimicrobial peptides that can be harnessed and tuned as per our needs. Proper utilization in pharmaceutical industry is only possible with mechanistic understanding of their mode of action at the molecular level. Design of peptidomimetic compounds based on molecular level understanding is desired. Such efforts should be welcomed by researchers in the field to eventually lead to nontoxic drugs for fatal diseases and drug delivery systems for enhanced bioavailability.

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