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Antibiotic-Peptide Conjugation Against Multi-drug Resistant Pathogens: A Comprehensive Review for Therapeutics and Drug Delivery Strategies

Karuppanan Kalimuthu[1] · N. R. Srinivasan[2] · G. Govindarajan[3]

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Abstract
A global public health crisis has been created by the emergence of serious infectious illnesses, the rising prevalence of infections that are impenetrable to antibiotics (AMR), and an inadequate supply of novel antibiotics. The expansion of antimicrobial drugs with unique molecular scaffolds is a time-consuming and cost-effective approach at the recent trend. On the other hand, the long-term exploitation of conventional antibiotics sparked the emergence of "superbugs" that are multi-drug resistant and are responsible for more deaths than HIV. Antimicrobial peptides (AMPs) are short peptides of natural innate defensive role against invading pathogens. Due to their broad spectrum of activity and low tendency to bacterial resistance, it can be recognized as one of the most potential antimicrobials. AMPs are opposed to conventional antibiotics, and it has their own benefits. AMPs use a wide range of mechanisms to exert their effects, including cell membrane damage, DNA fragmentation, impair macromolecule synthesis, damage to cell organelles, enzyme inhibition, and potential antimicrobial activity through immune regulation mechanisms. The main drawback of employing AMPs is the natural occurrence and are less stable and more toxic. Hence, to maintain this short-lived peptide's stability and multifunctional action, small-molecule antibiotic-peptide conjugates (APCs) are crucial. This review focuses on the types, mechanisms, pharmaceutical applications, and APCs approach to treat infections with multiple drug resistance and concludes the potential of AMPs in biomedical practice and in drug delivery.

Keywords AMR · AMPs · Antibiotics · MRSA

Introduction

According to the World Health Organization (WHO), antimicrobial resistance is a significant worldwide health issue, and it poses the greatest threat to human health today. The top priority is to find broad-spectrum antibiotics with little potential for bacterial resistance development. Antimicrobial peptides (AMPs) are appealing new antibacterial alternatives to traditional antibiotics for combating multidrug-resistant microorganisms (Falanga et al. 2016). Prokaryotes and eukaryotes are capable of producing AMPs (Bednarska et al. 2017). The 1980s saw the initial discovery of AMPs, which were short peptides produced by living organisms in nature, including bacteria, fungus and plants. Promising AMPs are identified from *Bacillus* spp, which show broad spectrum inhibitory activity against a panel of pathogens (Mora et al. 2011; Baindara et al. 2013). Similarly, an AMP has been isolated from *Propionibacterium jensenii* (Dziuba and Nalepa 2012). As of now, 3791 AMPs are reported from six kingdoms (Kang et al. 2019a). These groups of AMPs are classified based on size, net charge, structural properties, stability and solubility (Elias and Choi 2005). AMPs have broad spectrum activity against a wide range of bacteria (Bahar and Ren 2013; Zanetti 2004). Compared to classical antibiotics, the mode of action of AMPs is distinct, particularly in terms of membrane permeability (Lei

✉ G. Govindarajan
govind2610@gmail.com

[1] Department of Biotechnology, School of Bioengineering, SRM Institute of Science and Technology, KTR campus, Chennai, Tamil Nadu 603203, India

[2] Department of Mechanical Engineering, Sri Shanmugha College of Engineering and Technology, Sankari, Salem District, Salem, Tamil Nadu 637304, India

[3] Department of Chemistry, Sri Shanmugha College of Engineering and Technology, Sankari, Salem District, Salem, Tamil Nadu 637304, India

et al. 2019). There are diverse models that can be explained by the mechanisms of action of these peptides (Som et al. 2008). The amphiphilic nature of peptides enabled them to destabilize the bacterial membrane barrier via interacting with bacterial cell membrane (Chen et al. 2007). Nowadays, AMPs are used to treat bacterial infection, inflammation, and wound healing (Costa et al. 2019; Mahlapuu et al. 2016). Among all, are taken to AMPs clinical trials for cancer treatment (Zhang et al. 2021a). However, the natural peptides are not stable, and its toxic effect consistently persist. To open for potential clinical applications, it is essential to synthesize and optimize AMPs to overcome the disadvantage of natural peptides and generate therapeutic regimens more efficiently. On the other hand, antibiotics substances are more effective against a range of pathogenic bacteria (Kościuczuk et al. 2012; Moravej et al. 2018). Furthermore, antibiotic abuse and overuse result in the loss of antibiotic efficacy over time and the emergence of multidrug resistance (Lau et al. 1860). These AMPs are more stable when they undergo chemical modification such as cyclization, hybridization, isomerization, sequence alteration, peptidomimetics and nanoformulations and maintain their biological activity during inimical conditions (Mahlapuu et al. 2016; Yang et al. 2021). For instance, different nanoparticles and AMPs with various combinations can exert strong biological activity and stability against protease containing environment (Yang et al. 2021; Thapa et al. 2020). Designing novel AMPs and combining them with currently available small molecules (antibiotics) is one potential approach for addressing the complex AMR challenge. In contrast to conventional, expensive, and time-consuming screening of new antimicrobial agents, small molecule-peptide conjugates have excellent mechanisms to eliminate the emergence and spread of current antimicrobial-resistant threats. The main topics of this review are the origin, types, structural characteristics, stability, and mechanism of action (MOA) in relation to small molecules. Furthermore, it discusses the combination of AMPs with antibiotics due to their stability and broad-spectrum activity for more clinical usages.

Antimicrobial Peptide Sources

AMPs are found in prokaryotic and eukaryotic organisms, such as microorganisms, plants, amphibians, birds, mammals, and invertebrates (Yazici et al. 2018; Moyer et al. 2019; Braun et al. 2018; Wang et al. 2020; Li et al. 2019a; Lee et al. 2019). It can be categorized based on the sources (natural origin) as per APD3 (manually listed database of AMPs) (Wang 2022). Quite interestingly, there are 335 peptides from bacterial origin, 13 peptides from fungi, 8 peptides from protists, 4 peptides from archaea, 342 peptides from plants, and 2200 peptides from animals, along with synthetic peptides. In total, 5000 AMPs have been discovered or synthesized so far.

AMPs from Mammalian Source

Mammalian AMPs are identified in humans, cattle and other vertebrates. Amongst, defensins and cathelicidins are the major type of AMPs in the mammalian system (Huan et al. 2020). Defensin, a type of AMPs, has been identified in the leukocytes of rabbits (Hirsch 1956). Cathelicidins are another type of AMPs with distinct peptide length, amino acid residue and conserved domain (Harten et al. 2018). This group of peptides is obtained in neutrophils and macrophages in an inactive form and activated via the processing of leukocytes (Ageitos et al. 2017). Lactoferrin, a dairy AMP has been identified from cow milk (Groves et al. 1965), and other AMPs are obtained by enzymatic hydrolysis of milk (Huan et al. 2020). AMPs derived from human milk play a crucial role in breastfeeding to eshew infant morbidity and mortality. It is quite Interesting to note that, Casein 201 derived from β-casein has been found in human colostrum (preterm and term) (Zhang et al. 2017). Furthermore, human host defensive peptide (HDPs) lysosomes were derived from Human leukocytes (Zeya and Spitznagel 1963) and AMPs consisting of low molecular weight which are derived from the female genital tracts (Sharma et al. 2011).

AMP Derived from Microbial Origin

AMPs are also obtained from microorganisms such as bacteria and fungi. For instance, a wide variety of *Bacillus* strains secreting AMPs with potential broad spectrum activity against a panel of pathogens; *Salmonella, Shigella, Staphylococcus aureus* and *E.coli* (Mora et al. 2011; Baindara et al. 2013; Naimah et al. 2017). Similarly, *Propionibacterium jensenni* produced AMPs a propionicin are identified (Holo et al. 2002), and antibacterial battacin a cyclic AMPs are discovered from *Paenibacillus tianmuensis* (Oshiro et al. 2019). Nisin is the famous AMP identified from bacteria, originally synthesized by the host defense system to suppress other bacterial growth to compete nutrients in the ecological niches (Mattick and Hirsch 1947). Recently, nisin has broadly been used as an antiseptic in the food industry (Gharsallaoui et al. 2016; Shin et al. 2016; Kitagawa et al. 2019). It can be seen from the literature that intestinal microbiota is a fruitful origin of AMPs. Recent reports show that intestinal microbiota identified as a fruitful origin of AMPs (Garcia-Gutierrez et al. 2019; Pushpanathan et al. 2019). Daptomycin and vancomycin are well-known AMPs produced from actinomycetes species. Pargamicins types B, C and D are derived from *Amycolatopsis* sp. ML1-hF4 (Hashizume et al. 2017).

Similarly, a novel lipopeptide arylomycin A6 produced by soil derived *Streptomyces parvus* (Rao et al. 2013). Recently, temperature stable small peptide glycocin (an unusual property) is derived from thermophilic bacterium (Kaunietis et al. 2019). In addition to this, fungi have also been found to produce a unique AMP (Yazici et al. 2018). Interestingly, the mushroom (*Coprinopsis cinerea*) secretes copsin, a peptide that exhibits excellent activity against Gram-positive bacteria (*Enterococcus faecalis and Listeria monocytogenes*) by inhibiting their cell wall mechanism. (Essig et al. 2014).

AMPs from Marine Sources

Besides, marine derived AMPs are more attractive natural peptides with promising bioactivities (Huan et al. 2020). Discodermin A, cyclic AMPs derived from marine sea sponge and invertebrates mainly depends on innate immunity which is used as front line host defense mechanism to protect entry of pathogens (Gourbal et al. 2018). These AMPs primarily occur in the hemolymph, skin mucosa, and other body tissues. A potential wider spectrum of active AMP cecropins are isolated from hemolymph of *Hyalophora cecropia* (Wu et al. 2018). Marine derived AMPs are grouped under four categories based on biochemical nature and structure without accounting their mode of action (Erdem Büyükkiraz and Kesmen 2022). Thus, marine derived AMPs are structurally and functionally different from soil AMPs due to the extreme environment conations (salinity, tidal forces, pressure, etc.) (Falanga et al. 2016).

AMPs Derived from Plant

Plants also produce AMPs to show natural defence against pathogen invasion in the soil and air. Plant derived AMPs are grouped based on their amino acid residues, number of cysteine, identity and spacing (Lay and Anderson 2005). Based on the charge plant, AMPs are further classified as anionic and cationic peptides (Barbosa Pelegrini et al. 2011). There are diverse family of AMPs including defensins, thionins and cyclotide from plant origin (Srivastava et al. 2021). Amongst, Thionins are most abundant in seeds, leaves, roots and stem of the plants (Höng et al. 2021). Plant defensins have been isolated form leaves, flowers, tubers and pods (Ghag et al. 2012; Lay et al. 2003; Terras et al. 1995). Cysteine rich residues (CRPs) of plants based AMPs play an important role in structural stabilization via participation in multiple disulphide bridges (Tang et al. 2018). The primary function of the CRP is defence system in response to pathogen invasion and it shows activity against insect-larvae and enzyme inhibitory activity (Zhu et al. 2017; Colgrave and Craik 2004). Recent reports show that more than 3300 types of AMPs have been identified from various range of biological sources. AMPs from natural resources are summarized in Table 1.

Classification of Peptide

AMPs are classified into four major groups based of common secondary structures such as α helical, β sheet, α β mixed, and non-αβ peptides (Nguyen et al. 2011).

α-Helical Peptides

One of the largest class of AMPs is α helical peptide, which is well studied (Yan et al. 2022). Usually, AMPs consist of 12 to 54 amino acids residues with cationic properties at physiological pH (Mookherjee et al. 2020).

Moth cecropin, frog magainin, human cathelicidin LL-37 and melittin from bees are prominent examples of cationic peptide which belongs to amphipathic α helical peptides (Andersson et al. 2003; Agerberth et al. 1995). α helix peptides in aqueous solvent exhibit in irregular shape, but on the cell membranes, they undergo folded conformation. Generally, 50% of amino acid residues are hydrophobic, which is involve in amphipathic conformation and supports target membrane interaction (Hollmann et al. 2018). This peptide also contains disulfide bridges, in which N-terminal regions are amphipathic α helix and C –terminal regions have disulfide bridges, namely brevinin 2 and gaegurin (Almeida et al. 2012). These groups of peptides are more affinity towards cell membranes, which collapse the membrane organization through pore formation (Shai 1999). The antibacterial activity is impaired when α helix undergoes amino acid substitutions (Tossi et al. 1994). In the inactive form, AMPs do not exhibit α helical conformation, e.g. Magainin. Besides the separate activity of α helix, it also synergizes the antibacterial and cytotoxicity (Pino-Angeles et al. 2016).

β-Sheet Peptide

The second group of peptides exhibit β sheet conformation stabilized by two or more disulfide bridges with pairs of cysteine residues (Yan et al. 2022; Hollmann et al. 2018). Disulfide bridges in peptides can maintain overall stability and biological activity under various physiological conditions such as pressure, temperature, and serum (Osborn et al. 1995; Panteleev et al. 2015). Like, α helical peptides, the non-polar and polar groups exist in clusters on structurally unpaired surfaces of the peptide. Based on the structural characteristics, they are further sub-grouped into β hairpin, α, β and cyclic θ defensins (Yan et al. 2022). β hairpin

Table 1 Antimicrobial peptides from natural resources

S.no	Peptide name	Source	Number of AA residues	Antimicrobial activity	References
Microbial derived AMPs					
1	Alamethicin	*Trichodermaviride*	20	Gram positive	Mills et al. (2017)
2	Carnobacteriocin B2	*C.piscicola*	48	Gram positive	Hammi et al. (2016)
3	Carnobacteriocin(BM1)	*C.piscicola* (*LV17B)*	43	Gram positive and negative	Tulini et al. (2014)
4	Circular in A	*C.beijerinckii* (ATCC 25752)	69	Gram positive and negative	Perez et al. (2016)
5	Divercin-V41	*C.divergens V41*	43	Gram positive	Brillet-Viel et al. (2016)
6	Enterocin	*Enterococcus*	70	Gram positive and negative	Ben Braïek et al. (2018)
7	Enterocin P	*E. faecium* P13	44	Gram positive	Le et al. (2014)
8	Ericin S	*Bacillus subtilis*	32	Gram positive	Sharma et al. (2018)
9	Gassericin-A	*L. gasseri LA39*	58	Gram positive and negative	Maldonado-Barragán et al. (2016)
10	Gramicidin A	*Bacillus brevis*	15	Gram positive and negative	Muhammad et al. (2016)
11	Hominicin	*Staphylococcus hominis MBBL 2-9*	21	Gram positive and negative	Ebrahimipour et al. (2014)
12	Lichenin	*Bacillus licheniformis*	12	Gram positive and negative	Bhat (2018)
13	Listeriocin 743A	*Listeria innocua743*	43	Gram positive	Kalmokoff et al. (2001)
14	Leucocin A	*Leuconostoc pseudomesenteroides*	37	Gram positive and negative	Chen et al. (2018)
15	Mesentericin Y105	*Leuconostoc mesenteroides*	37	Gram positive	Arakawa et al. (2016)
16	Microcin- J25	*E. coli* AY25	21	Gram positive	Mukhopadhyay et al. (2004)
17	Nisin	*Lactococcus lactis*	34	Gram positive	Mills et al. (2017)
18	Pediocin PA-1/AcH	*P. acidilactici* PAC-1.0	44	Gram positive	Araújo et al. 2016)
19	Planosporicin	*Planomonospora alba*	24	Gram positive and negative	Gajalakshmi (2017)
20	Plantaricin C19	*Lactobacillus* C19	37	Gram positive	Atrih et al. (2001)
21	Plantaricin A	*Lactobacillus plantarum*	26	Gram positive and negative	Jiang et al. (2018)
22	Plantaricin ASM1	*Lactobacillus plantarum* A-1	43	Gram positive	Hata et al. (2010)
23	Pyrulariathionin	*Pyrularia pubera*	47	Gram positive and negative	Guzmán-Rodríguez et al. (2015)
24	Subtilin	*Bacillus subtilis*	32	Gram positive	Singh et al. (2017)
25	Subtilosin A	*Bacillus subtilis*	35	Gram positive and negative	Babasaki et al. (1985)
26	Streptin 1	*Streptococcus pyogenes*	23	Gram positive	Wescombe and Tagg (2003)
27	Trtesin	*Fusarium tricinctum*	52	Fungus, Gram Positive	Tejesvi et al. (2013)
Insects derived AMPs					
1	Acaloleptin	*A.luxuriosa*	71	Gram positive and negative	Vogel et al. (2014)
2	Andropin	*D.melanogaster*	34	Gram positive	Abry et al. (2017)
3	Apidaecin IA	A. *mellifera*	18	Gram positive	Farouk et al. (2017)
4	Cecropin	*H. cecropia*	37	Gram positive	Lee and Lee (2015)
5	Defensin- α	*A.aegypti*	40	Gram positive and negative	Price et al. (2015)
6	Drosomycin	*D.melanogaster*	44	Fungus	Zhang and Zhu 2009)
7	Holotricin	*H.diomphalia*	43	Gram positive and negative	Lee et al. (1995)
8	Sapecin- α	*S. peregrine*	40	Gram positive and negative	Manabe and Kawasaki (2017)
9	Tenicin 1	*T.molitor*	43	Gram positive and negative	Yang et al. (2018)
10	Thanatin	*P. maculiventris*	21	Gram positive and negative	Duwadi et al. (2018)
Plant derived AMPs					
1	Hevein	Latex of rubber trees	43	Fungus	Parijs et al. (1991)
2	Psacotheasin	*Psacotheahilaris*	34	Fungus, bacteria	Hwang et al. (2010a, b)
3	Purothionins	Wheat endosperm	45	Gram positive and negative	Höng et al. (2021)
4	Snakin-1	Potato tubers *Solanumtuberosum*	63	Fungus, Gram positive and negative	Segura et al. (1999)

Table 1 (continued)

S.no	Peptide name	Source	Number of AA residues	Antimicrobial activity	References
5	Snakin-2	Potato tubers *Solanum tuberosum cv Jaerla*	66	Fungus, Gram positive and negative	Berrocal-Lobo et al. (2002)
AMPs from animals					
1	Androctonin	*Androctonus australis*	25	Gram positive and negative	Panteleev et al. (2017)
2	Bactenecin	*Bovine Neutrophiles*	12	Gram positive and negative	Young-Speirs et al. (2018)
3	Brevinin	*Ranabrevipora porsa*	24	Gram positive and negative	Savelyeva et al. (2014)
4	Buforin II	*Bufo gargarizans*	21	Fungus, Gram positive and negative	Sun et al. (2015)
5	Cupiennin 1a	*Cupiennius salei*	35	Gram positive and negative	Pukala et al. (2007)
6	Dermaseptin S1	*Phyllomedusa sauvagii*	34	Gram positive and negative	Belmadani et al. (2018)
7	Lycotoxin	*Lycosa carolinensis*	27	Gram positive and negative	Tahir et al. (2017)
AMPs from humans					
1	A defensins	Human neutrophils	12–80	Fungus, Gram positive and negative	Schaal et al. (2018)
2	Cathelicidins	Human neutrophils	30	Fungus, Gram positive and negative	Sheehan et al. (2018)
3	Human Histatin 8	Human	12	Fungus, Gram positive and negative	Khurshid et al. (2017)
4	LL37 Neutrophils	Human	37	Fungus, Gram positive and negative	Baxter et al. (2017)

structure can be formed via antiparallel β sheet linked by the turn of 3 to 4 amino acids e.g. Hepcidins (Edwards et al. 2016). A few AMPs, namely tachyplesin-1, polyphemusin-1, gomesin, arenicin-3, consist of β hairpin structure with two disulfide bridges (Erdem Büyükkiraz and Kesmen 2022). AMPs, such as lactoferricins, bactenecins, and arenicins, have single disulfide bonds. The primary effect of these disulfide bonds is maintaining structural stability and protecting the AMPs from degradation (Panteleev et al. 2015). These AMPs with no helical conformations are found in fungi, insects, plants and vertebrates (Weerden et al. 2013). Defensins are the most important members of this family of AMPs, and the disulfide bond connectivity of cysteine residues further determines the class of defensins. They are α, β, and cyclic θ defensins, all of which contain a β sheet structure. Among them, θ defensins are cyclic peptides with a cysteine ladder (Cyclic) conformation, which provides antimicrobial activity and also participates in the structure and overall stability of the cyclic scaffold (Conibear et al. 2014). The planar features and strong stability of cyclic peptides can facilitate the development of peptide drugs with wider bioactivity and specificity (Falanga et al. 2017).

Mixed (α, β) and Non (α, β) Peptides

Several groups of AMPs acquire α-helix and β-sheet conformations, which are stabilized by three or four disulfide bonds. The cysteine-stabilized α and β structure consist of single α helix and β stands (2 or 4 antiparallel fashion) has been first discovered from insects defensins and neurotoxins from scorpion (Hill et al. 1991). The mixed αβ AMPs architecture has been constructed by three β sheet and short helix in the N-terminus, e.g. human β defensin-3 (Dhople et al. 2006). Interestingly, cysteine stabilized mixed αβ (CS-αβ) from plants derived defensins show good activity against fungi instead of antibacterial active insect defensins. However, CS-αβ- motif is unclear, but this type AMPs have common mode of action, such as inhibition of cell wall biosynthesis and interaction with lipids II (Dias Rde and Franco 2015). In addition, Non- αβ AMPs are another class of peptides lacking true secondary structure (Yan et al. 2022). These classes of peptides are called residue rich peptides namely, trptophan (Indolicidin), serine, glycin, proline (arasin 1), threonine and histidine (histatin) and they show flexibility in aqueous solution (Yan et al. 2022; Helmerhorst et al. 2005; Paulsen et al. 2013). They possess membrane invasion characteristics by interacting with the cationic choline head group of the lipid bilayer through the formation of hydrogen bonding of lipid bilayer components (Chan et al. 2006). Among these, Indolicidin peptide derived from bovine neutrophils inhibits DNA replication and promotes the filamentation of bacteria via strong interaction with the negatively charged phosphate backbone of DNA (Hsu et al. 2005). Other than this class of AMPs, a short fragment also exists from antimicrobial proteins that are naturally occurring with wider antibacterial activity (Starling 2017;

Ragland and Criss 2017; Zhang et al. 2018). It contains 133 residues with α helix, and β sheet in the protein architecture. Recently, arginine-rich NEMURI protein encoded by fruit flies genome has been identified as immune-modulatory effect with potential antibacterial activity (Toda et al. 2019). Moreover, some peptides have metal ions (Cu^{2+} and Ni^{2+}) (ATCUN) binding motif, with high bind affinity (Portelinha et al. 2021). Interestingly, Cu^{2+} (ATCUN) can participate in ROS generation (Wende and Kulak 2015; Heinrich et al. 2019).

Mechanism of Action

The antimicrobial effect of the AMPs mainly depends on two mechanisms such as membrane targeting (Loss of membrane integrity) and non-membrane targeting (inhibition of DNA and other biomolecule synthesis) (Erdem Büyükkiraz and Kesmen 2022). Due to the cationic nature of AMPs, they bind via weak vanderwaals interactions with anionic charged bacterial cell membrane (Hollmann et al. 2018). The negative charge of the bacterial membrane is maintained by biomolecules like lipoteichoic acid and lipopolysaccharides (Scott et al. 1999) whereas animal contains a zwitterionic phospholipids (Posphatidylcholine, sphingomyelin and cholesterol, which facilitates AMPs to interact with the bacterial membrane (Matsuzaki 1999; Gaspar et al. 2013). Unlike conventional antibiotics, AMPs have a unique MOA that inhibits the further development of bacterial resistance (Pfalzgraff et al. 2018). Based on the MOA, this can be further divided into three types they are viz membrane disruption, interference of metabolic reactions and immunomodulation (Brogden 2005; Liang and Diana 2020). In the membrane disruption mechanism, AMPs initially attach to the cell membrane of pathogens through electrostatic forces, leading to membrane permeabilization. Subsequently, cell membrane integrity is lost, resulting in drastic changes in membrane potential, leakage of intracellular constituents, and ultimately leading to cell death (Costa et al. 2015)-(Reinhardt and Neundorf 2016). Generally, the action of AMPs on cell membrane disruption has been suggested by three models such as barrel-stave, toroidal-pore, and carpet models (Mookherjee et al. 2020; Brogden 2005).

Barrel-Stave Model

In the barrel-stave model, AMPs form bundles attached to the cell membrane to form hydrophilic pores and lipid interaction by hydrophobic residues. As a result, hydrophilic residues face the pore channels (Yan et al. 2022; Kang et al. 2014; Luca et al. 2014). In extreme conditions, AMPs trigger cell membrane damage, resulting in cell death (Lohner and Prossnigg 2009). Alamethicin is the best example of pore-forming AMP.

Toroidal-Pore Model

In the toroidal-pore model, AMPs aggregate on the surface of the membrane, which promote the membrane to bend substantially via pore. As a result, pore build-up takes place by the interaction of peptides and lipids. This mechanism is similar to the barrel-stave model but lipid–peptide interaction instead of peptide-peptide (Nguyen et al. 2011; Yan et al. 2022). These peptide conformations induce localized membrane deflection, occupying an equal proportion of peptides and phospholipids due to the formation of a 'toroidal pore' (Shahmiri et al. 2016). For instance, magainin 2, arenicin, and lacticin Q were used in this model to illustrate the MOA. Additionally, some positively charged peptides, such as TC19, TC84, and BP2, undergo membrane arbitration by initiating fluid domains (Omardien et al. 1860).

Carpet-Like Model

In the Carpet-like model, AMPs enfold in an entire membrane surface, as the name suggested, without forming pores (Bechinger 1999; Pouny et al. 1992; Lee et al. 2016). They may induce tension on the bacterial membrane, leads to membrane disorganization and micelle formation (Shai 1999; Ladokhin and White 2001). Neither pore formation nor penetration of peptides into the (hydrophobic) membrane occurs. This action can induce membrane lysis either partially or completely, eventually leading to cell death consequently (Zhang et al. 2021b). Cathelicidin LL-37, derived from the human body, exerts activity using this mechanism, and β-sheet plays an important role in this model (Shenkarev et al. 2011; Corrêa et al. 2019).

Aggregate Model

Besides these models, the aggregate model is also proposed in which peptides strongly interact with the anionic cell membrane, facilitating the formation of complex lipid-peptide micelle (Hale and Hancock 2007) (Fig. 1). This transmembrane aggregates AMPs, lipids, and water, unlike the carpet model. It can promote ions and intracellular elements leakage through channel formation, resulting in cell death. These channels also help AMPs move further into the cytoplasm and interact with other molecular targets based on killing action. This model provides further insight into cationic peptide translocation across the cell membrane and their activity with intracellular molecules (Hancock and

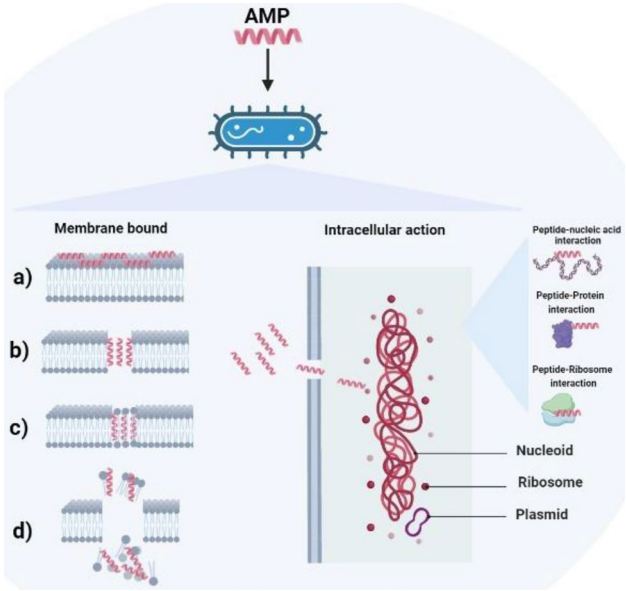

Fig. 1 The AMP counteracts with the bacteria either directly through membrane bound action or intracellularly by transporting across the cell membrane. The AMP works membrane bounded through four different ways: **a** accumulation of parallelly arranged AMP over cell membrane in a carpet like manner having their hydrophobic region facing the phospholipid and the hydrophilic region facing the aqueous content. Increased accumulation of AMP causes disruption and damage to the cell membrane in detergent-like action. **b** In the barrel-stave model the AMP aggregate together in a barrel-like manner arranged parallel to the phospholipid bilayer and create an ion channel which causes cytoplasmic leakage and cell death. **c** The toroidal pore model/wormhole models the AMP embedded into the cell membrane and forms a toroidal pore complex through lipid-AMP interaction. **d** In case of cationic AMP form lipid-peptide micelle complex which creates a channel and causes leakage of all intracellular content and leading to cell death. This mainly helps in the transport of AMP across the cell membrane to interact with cytoplasmic contents. The intracellular AMP action happens by inhibition of protein synthesis, inhibition of nucleic acid synthesis and inhibition of cell division or cell wall formation

Patrzykat 2002). Other than the proposed membrane model, some AMPs disrupt cell membranes by electroporation and alteration of membrane component distribution (Gan et al. 2021; Nayab et al. 2022).

Non-membrane Mechanism of AMPs

Instead of membrane action, some AMPs interact with targets at intracellular levels (Erdem Büyükkiraz and Kesmen 2022). AMPs translocate across the cell membrane through a binding process with intracellular targets. They subsequently disrupt important metabolic processes such as nucleic acid (DNA, RNA) synthesis, inactivation of specific enzymes, protein synthesis, and cell wall synthesis (Brogden 2005). Proline-rich AMPs exhibit intracellular activity by preventing bacterial protein biosynthesis in the protein synthesis inhibitory mechanism. For instance, AMPs bactenecin 7 and Tur1A show translation inhibitor action by arresting the transition from initiation to elongation (Mardirossian et al. 2018). Additionally, a few AMPs have different targets. For example, the insect-derived AMP apidaecin inhibits protein biosynthesis by preventing a releasing factor on the ribosome (Florin et al. 2017). Another peptide, namely DM3, can target crucial intracellular pathways of the translation process (Le et al. 2016). PrAMPs, pyrrhocoricin, and drosocin hinder protein folding pathways by binding specifically (DnaK, HSP) and nonspecifically (GroEL) to bacterial chaperonin (Le et al. 2017; Wrońska and Boguś 2020).

Several AMPs possess antimicrobial activity by interacting with DNA and RNA. The buforin II AMP, derived from frogs, translocates across the membrane and prevents nucleic acid biosynthesis (Park et al. 1998). Likewise, Indolicidin inhibits DNA biosynthesis without causing membrane permeability (Cardoso et al. 2019). Additionally, a few AMPs indirectly inhibit bacterial DNA replication and RNA synthesis (Kang et al. 2018; Wu et al. 2019). Many AMPs participate in metabolic inhibitory activity. Peptide eNAP-2 inhibits elastase and serine proteases of microbial origin (Le et al. 2017). Cathelicidin-BF, from the venom of *Bungarus fasciatus* hampers thrombin-mediated platelet aggregation and inactivation of protease-activated receptor 4 (Shu et al. 2019). Many AMPs block cell division by preventing DNA replication and SOS response (DNA damage). This disrupts the cell cycle, or chromosome segregation (Lutkenhaus 1990). MciZ, a short residue, is reported as an effective bacterial cell division Z-ring formation and localization inhibitor (Cruz et al. 2020). Additionally, AMPs also affect bacterial adhesion through the adsorption of biomaterial surfaces and they are involved in the prohibition of cell-to-cell communication, and down-regulate the essential genes for biofilm formation (Batoni et al. 1858; Brackman and Coenye 2015; Fuente-Núñez et al. 2012; Pletzer et al. 2016). Some AMPs have immune-modulatory effects as host defense peptides that protect from pathogen invasion by activating various immunological responses (Hancock et al. 2016; Mack and Kim 2016; Kang et al. 2019b). AMPs can regulate different cell receptors, such as cytokine receptors, chemokine receptors, and Toll-like receptors (Zhang et al. 2021a). AMPs are part of the immune system, associated with immune cells to suppress the growth of pathogens and control infection. The immune cell-mediated action of AMPs is extremely complex (Fruitwala et al. 2019). Hence, immuno-modulatory AMPs also stabilize cellular homeostasis by preventing infection-mediated tissue damage (Zhang et al. 2021a). Recent reports reveal that amyloids and amyloidogenic peptide-mediated direct co-aggregation are the foremost antibacterial mechanisms of AMPs (Kurpe et al. 2020).

Therapeutic Potential of AMPs

AMPs exhibit various bioactivities such as, antibacterial, antiviral, antifungal, immunomodulatory, tumor modulatory and antiparasitic activities (Liang and Diana 2020; Mokoena 2017; Liang et al. 2020; Struyfs et al. 2021; Kückelhaus et al. 2009). AMPs are considered as potential alternatives for existing antibiotics, due to their low tendency to develop drug resistance. These therapeutic activities support AMPs as a potential drug candidates for pharmaceutical application (Kang et al. 2017). They may be used alone or with other small molecules like antibiotics to achieve good action against pathogens (Gordon et al. 2005). Gramicidin A, is first AMP derived from gram positive *Bacillus subtilis* and was commercialized in the 1940s (Herrell and Heilman 1941). Even today, the AMPs used to treat topical issues like wounds, eye, nose and throat infections. However, Gramicidin A cannot be used internally due to their severe hemolytic toxicity (Subbalakshmi and Sitaram 1998). In 1953, Nisin was commercially marketed as an antimicrobial compound which can be used as a food preservative (Gharsallaoui et al. 2016).

The potential activities have also expanded for multidrug resistance pathogens, oral infections, and cancers, providing good results when combined with other drugs (Shin et al. 2016). The US food and drug administration (FDA) approved a cyclic peptide Daptomycin in 2003 against multi drug resistance pathogens for topical application (Carpenter and Chambers 2004). Similarly, FDA-approved semisynthetic peptides, Dalbayacin, telavancin and Oritavancin are derivatives of vancomycin between 2009 and 2014 for skin-associated infections. Other peptides, such as polymyxins (Colistins), a cyclic lipopeptide approved in the 1950s for treating MDR Gram-negative bacterial infections (Erdem Büyükkiraz and Kesmen 2022; Yan et al. 2022). As of now, more than 60 peptides have been approved FDA and more than 400 peptides are under clinical trials (Mousavi Maleki et al. 2022).

Synthetic analogue of cationic peptide indolicidine, Omiganen pentahydrochloride -MBI-226 were examined against 1437 clinical isolates and 214 clinical yeasts (Sader et al. 2004). Phase III clinical trials have been successfully completed for rosacea treatment. Hence, exposure to AMP with low concentration after long time facilitates bacterial resistance. High concentration has been recommended for stable bactericidal activity (Rodríguez-Rojas et al. 2021). The AMP also exerts antifungal activity (Lucca and Walsh 1999). Antifungal AMPs interact with fungal cell surfaces and target intracellular components, leading to the development of reactive oxygen species (ROS), mitochondrial dysfunction, apoptosis, and impairment of cell cycles (Struyfs et al. 2021). AMPs, named VLL-28, possess antifungal activity against Candida species, both biofilm and planktonic cells (Roscetto et al. 2018). Some AMPs containing histidine-rich residues have potential antifungal activity. These peptides enter fungal through cells either membrane receptors or transmembrane mechanism. These peptide groups target intracellular organelles, such as mitochondria, without damaging cells, inhibiting mitochondrial respiration, and subsequent cell death were occurred (Li et al. 2019a; Dhir et al. 2018). P113 is an AMP in saliva, which has strong activity against *Candida albicans* and other bacterial pathogens (Haney et al. 2021; Yu et al. 2017). This peptide is also used for treating oral Candidiasis in HIV patient's treatment. Furthermore, AMPs have also shown strong antiviral potential with low toxicity, making them helpful in treating viral infections through either host -targeting or virus-targeting mechanisms (Erdem Büyükkiraz and Kesmen 2022; Castel et al. 2011). The epidemic and pandemic scenario induced by viral strains pose a notorious and growing threat in the world (Erdem Büyükkiraz and Kesmen 2022). Bovine antimicrobial peptide-13 exhibits activity against enveloped viruses. These AMPs potentially reduce the transmissible gastroenteritis viral multiplication by inhibiting gene expression and protein synthesis (Liang et al. 2020). The AMPs LL-37 exert activity against different types of enveloped viruses such as Human immunodeficiency virus (HIV), dengue virus (DENV), and Zika virus (ZIKV) through disruption of viral membrane and DNA replication process (Ahmed et al. 2019; Barlow et al. 2011; Tripathi et al. 2013). Likewise, various studies have examined Anti-SARS-COV response for heptad repeat (HR) peptides against these viruses (Outlaw et al. 2020; Xia et al. 2020). OC43-HR2P peptide derivative, EK1, exerts wider activity against multiple human coronaviruses (HCoVs). On the other hand, the HRC domain of SARS-Cov-2S, when conjugated with tetra-ethylene glycol-cholesterol synthesis lipopeptide derivative, impaired virus-mediated cell–cell fusion and halted new infection (Outlaw et al. 2020). In another study, DP7 (VQWRIRVAVIRK) peptide antiviral properties has been demonstrated (Zhang et al. 2021a). The study depicts that DP7 has a strong inhibitory effect on SARS-CoV and SARS-CoV-2 viruses through ACE2 receptor mediated action. Zhang et al. also shows that a concentration of (104 µg/mL and 73.625 µg/mL concentration of DP7) is needed (50% inhibitory concentration) to suppress SARS-CoV and SARS-CoV-2 pseudovirus (Zhang et al. 2021a).

AMPs have demonstrated the ability to selectively kill cancer cells by interacting with the cancer cell membrane (Kang et al. 2017; Nel et al. 2009). Anionic lipids on the outer leaflet of cancer cell membranes facilitate the binding specificity of cationic AMPs on these surfaces (Portelinha et al. 2021). In tumor therapy, classical chemotherapeutic agents often kill cancer and normal cells, leading to severe side effects in patients. However, cationic AMPs

exhibit more specific action against target cancer cells such as cell membrane, mitochondria, nucleus lysosome and chromosomal DNA, while sparing normal cells (Rathinakumar et al. 2009; Wang et al. 2017). Numerous studies have shown that AMPs are sensitive to cancer cell but harmless to normal cells (Wang et al. 2008). AMPs can target tumour-specific cells and it can be utilized for current and future cancer treatments (Jin and Weinberg 2019). These peptides strongly attach to the acidic phospholipids on the outer surfaces of the tumour cells, leading to drastic metabolic changes in the tumor cells, such as alteration membrane potential, and cytoskeleton. It results in cell death through the formation of pores and leakage of intracellular components (Mahlapuu et al. 2016; Jäkel et al. 2012). AMPs have emerged as attractive agents for tumor therapy. For instance, the HPRP-A1 peptide derived from *Helicobacter pylori* has exhibited anticancer activity (Zhao et al. 2013). Moreover, combining HPRP-A1 with a homing peptide (iRGD) has improved anticancer activity, where the homing peptide aids the penetration of HPRP-A1 into A549 MCS (Hu et al. 2018). Similarly, the peptide (L-K6) kills MCF-7 type cancer cells through nuclear convulsion rather than cell surface-mediated mechanism (Hancock et al. 2016).

Certain AMPs also protect hosts from bacterial infection through the immune modulatory effects (Hancock et al. 2016; Kang et al. 2019b; Zasloff 2019). The role of AMPs in immune regulation process is more complex (Zhang et al. 2021a). Numerous cationic peptides have been examined and it found to have potent immunomodulatory responses with two rationales; the ability to induce chemokines and suppress the liberation of pro-inflammatory cytokines (Haney et al. 2015; Reffuveille et al. 2014). Different ways have been associated with the immunomodulation process, including reduced endotoxin-induced inflammatory response, synthesis of pro-inflammatory factors, adaptive immunity response, synthesis of cytokines, and involvement of macrophages to exhibit immune modulatory action (Moravej et al. 2018; Haney et al. 2019). For example, clavanin MO, a derivative of clavanin A peptide, incorporates a hydrophobic amino acid into the conserved oligopeptide FLPII, resulting in dual properties of antimicrobial and immune-modulatory effects in the same peptide (Silva et al. 2016; Sultana et al. 2021). AMPs such as clavanin-MO have been shown to elevate the synthesis of IL-10 and decrease IL-12 in exposed cells, indicating the ability to harmonize the innate immune system by requiring more leukocytes (Silva et al. 2016). Therefore, AMPs can have either pro- inflammatory or anti-inflammatory activity based on their production levels at the sites of inflammation (Prasad et al. 2019). Additionally, AMPs and their immuno modulatory actions inhibit infection-mediated tissue damage and maintain cellular homeostasis (Sultana et al. 2021). AMPs also exhibit a strong anti-inflammatory response. For example, the anti-inflammatory response of Melectin AMPs extracted from *M. albifrons* was examined by qRT-PCR (Ko et al. 2020).

Apart from these activities, AMPs have exhibited various other activities, including participation in natural immunity, phagocytosis stimulation, promoting the cell cycle of epithelial and fibroblasts cells (Moravej et al. 2018; Aisenbrey et al. 2019). AMPs have been found to stimulate the growth of wound granulation tissues and enhance wound healing properties (Mahlapuu et al. 2016; Taniguchi et al. 2019). The wound-healing activity of recombinant P-LL37 has been reported in dexamethasone-treated mice (Ramos et al. 2011; Silva et al. 2015). Furthermore, AMPs can induce human lymphocytes successfully to remove infected cells caused by viruses, bacteria, and cancer cells. They also play a significant role in chronic inflammation and aid in developing helper T cells, chemokine synthesis, elevation of the antibody IgG level, and stimulation of lymphocytes to eliminate infected cells (Zasloff 2019; Taniguchi et al. 2019; Lande et al. 2014). Some AMPs also play an important role in skin barrier and function, with the potential to treat skin-associated problems, such as acne, psoriasis, diabetic foot ulcer (Nguyen et al. 2020; Alencar-Silva et al. 2018). Additionally, AMPs have been linked to the occurrence and development of diabetes (Conlon et al. 2018; Zainab et al. 2019). Moreover, AMPs also play a key role in supporting colon homeostasis, tissue repair and preserving the colon micro biota (Yoshimura et al. 1950; Rathinam and Chan 2018; Zhang et al. 2019). Besides their therapeutic potential, AMPs have various other applications such as food industry as food additives, animal husbandry, aquaculture, and plant protection applications, to replace the chemical agents (Erdem Büyükkiraz and Kesmen 2022). For instance, *Streptomyces albulus* produced AMPs (ε-polylysinea homoplymer of L-lysine) has been approved by the FDA for food precautionary applications (GRAS) status due to their broad spectrum active potential (Luz et al. 2018). To maintain the scope of review we highlighted only therapeutic application of AMPs, and other applications were briefly described.

Antibiotics and Peptide Conjugates

AMPs are attractive and promising alternatives to classical antibiotics due to their potency, low tendency to develop resistance, and potential as biomolecule drug delivery vehicles (Splith and Neundorf 2011). However, certain limitations are associated with AMPs in clinical applications, such as low residence time in the bloodstream, toxicity, immunogenicity, sensitivity to host proteases, and other side effects (Moravej et al. 2018). On the other hand, naturally derived peptides are mostly unstable, and long-term clinical use of these AMPs may result in significant toxicity

in mammalian cells (Starr et al. 2018). Hence, design of peptides or modification of natural peptides with another type of biomolecules enhance their antibacterial activity with different mode of action, resulting in functionalized AMPs and AMP conjugates (Brogden and Brogden 2011). AMPs are functionalized to synthesise peptide conjugates by attaching substances via wider coupling methodologies. A common concept is to merge the modification at the α amino group to the carboxylic terminal, providing an amide linkage. Chemoselective coupling concept has been adopted to spawn conjugates for free peptide in solution where amino-reactive N-hydroxy succinimides or maleimide (thiol reactive) can be activated (Reinhardt and Neundorf 2016). This review highlights recent advances in synthesizing antibiotics coupled with AMP conjugates and novel activities. The important strategy is that existing antibiotics coupled with AMPs (covalently) can also induce synergistic effects on a wide range of bacteria. This combination strategy enhances antibacterial activity, reduces adverse effects, and requires lower doses (Yamauchi et al. 2022). The synergistic activity of APCs has been reported to overcome bacteria's existing antibiotics and AMP resistance (David et al. 2018). For example, Vancomycin-magainin conjugates have increased activity against only vancomycin-resistant Enterococci with better minimal inhibitory concentrations than antibiotic alone (Arnusch et al. 2012). These reports suggest that the length of amino acid sequences promotes the MOA on the bacterial membrane, in which shorter fragments adopt the carpet model mode, while longer peptides undergo to form transmembrane pores based on the mode of action (Arnusch et al. 2012). Similar to Vancomycin-peptide conjugates, Telvancin and Dalbavancin APCs are also approved by the FDA for antimicrobial therapy (Etayash et al. 2021). Levofloxacin conjugated with indolicidin (rich hydrophobic residues) via an amide bond has been tested to determine whether this combination impacts activity (Ghaffar et al. 2015). In this study, no improved activity has been observed by chosen linkage, whereas the activity is increased through a physical mixture of levofloxacin and indolicidin. This observation denotes that the amide linkage reduces the activity of levofloxacin (Ghaffar et al. 2015). Recently, ubiquicidin (UBI) a cationic peptide variant linked to chloramphenicol, which exhibits antibacterial activity against *E.coli* and *Staphylococcus aureus* (Chen et al. 2015a). The conjugation of chloramphenicol into UBI has been achieved via a glutaraldehyde linker. Many reports revealed that short peptide motif along with antibiotic drugs show positive antibacterial activity. For example, unique polycationic lysine-like substances are produced from modified neomycin B variants that enhance the antibacterial activity and also promote RNA binding affinity (Bera et al. 2011). Neomycin B consist of a hydroxyl residue (OH) at C5 position, which facilitates thr coupling of a short motif (Tryp-Tryp-Lys). This conjugation approach has obtained new antimicrobial activity (Zhang et al. 2008). In addition to this, amphiphilic nanostructures consist of hydrophilic surface and hydrophobic core molecule are derived from when neomycin is modified with short dehydropeptides (Yadav et al. 2014). Overall, these examinations reveal that the increased activity is achieved by physical mixture of AMP and antibiotic, whereas decreased activity is observed through the covalent conjugation of peptide and antibiotics (Ghaffar et al. 2015). Hence, the amalgamated approach itself is very effective. While preparing covalent conjugates, extra consideration should be taken to avoid toxicity and enhance activity. To achieve this, linker sites can be found within the structures of antibiotics to avoid the loss of antibiotics' activity while combined with AMPs. On the other hand, to get better activity of AMPs in terms of bacterial membrane interaction, it can be modified by a lipidation process with fatty acids (Chu-Kung et al. 2010). D-Amino acid instead of L-amino acid in AMPs can maintain more stability against proteases, which increase pharmacokinetic properties and improve their bioactivity (Li et al. 2016; Zhang and Yang 2022; Luong et al. 2020). In addition, structural engineering approaches such as terminal acetylatin, amidation, cyclization, and L to D amino acid residue substitution inhibits the proteolysis by various proteases and improve the bioactivity (Lu et al. 2020; Jia et al. 2017; Li et al. 2019b). Furthermore to achieve for better stability and target selectivity, nanotechnologies including electrospun nanofibers, liposomes or metal to AMPs, strengthen their overall properties (Tang et al. 2021; Biswaro et al. 2018; Rajchakit and Sarojini 2017). Combining of antibiotics and AMPs is still promising strategy to enhance various bioactivities by adopting suitable conjugation methodologies.

AMPs-Polymer Nano-structures for Drug Delivery

Nanotechnology furnishes the stability and sustained delivery of AMP to enhance the target selectivity. Nano-delivery cargo can improve the pharmacokinetics, bioavailability, and antibacterial efficacy of AMP (Radaic et al. 2020). Various types of nanostructures have been used for AMP delivery, such as carbon nanotubes, metal nanoparticles, liposome-based nanostructures, and polymeric substances (Carratalá et al. 2020). Generally, surfactant, lipid, and polymer-mediated drug delivery are well-developed.

Inorganic Materials

To increase the AMPs' efficacy, numerous delivery systems have been developed in which peptides are incorporated either covalently or non-covalently (Singh et al. 2016; Sandreschi et al. 2016). Nowadays, organic nanomaterials such as metal oxides, metals, mesoporous materials, and nano clays are attractive and effective drug delivery systems for peptides, proteins, and other biomolecules (Malmsten 2013). Organic nanomaterials also aid protection from enzymatic and chemical degradation, inhibition of aggregation, conformational changes, sustained drug release, promote bioavailability, and reduce toxicity. A quite few nanomaterials show antimicrobial activity, facilitating synergistic effects in combination with AMPs (Huh and Kwon 2011; Hajipour et al. 2012). Mesoporous materials are fascinating for the sustained release of drug molecules and can form mesoporous structures with a wide range of nanoparticles. The effect of nanoparticle porosity and charges, including drug loading and release of AMP LL-37, has been investigated on cell membrane disruption and antimicrobial activity (Braun et al. 2016). In addition, metal nanoparticles such as Au, Pt, Ag, and Cu afford greater response for drug delivery. With special reference to metal nanoparticles as an AMP drug delivery system, the nanodots (AuNDs) prepared by etching and co-precipitation of hybridized ligands and an AMP (Surfactin) and 1-dodecanethiol on Au nanoparticles result in enhanced antimicrobial activity against MDR strains when compared to surfactin alone (Chen et al. 2015b).

Hence, numerous quantum dots show cell toxicity (Malmsten 2013), limiting the usage of drug delivery vehicles. Nowadays, several types of quantum dots are of special interest as AMP delivery vehicles. For instance, ZnO quantum dot, AMP (UB129-41), and MPA based nanoparticle composites are increasing antibacterial activity with less cytotoxicity (Chen et al. 2015b). Carbon-based nanomaterials, namely graphene and carbon nanotubes (CNT), are of charming interest as drug delivery vehicles based on their tendency for aggregation in solution and stabilization via appropriate surface modification (Malmsten 2013). For example, when conjugated with graphene oxide membranes, nisin, a pore-forming AMP, results in 100% MRSA-killing (100%) activity that can be used for water disinfection (Kanchanapally et al. 2015).

Polymeric Substances

Polymers afford greater scope as drug delivery systems for various antimicrobial therapies due to their biocompatibility and potential synergistic activity (Kenawy et al. 2007). Polymers of repeated monomeric units are frequently used in medicinal applications. AMP polymeric nanostructures provide numerous benefits, including stability and bioactivities (Rai et al. 2022). RBRBR, a short peptide exerts enhanced antimicrobial effects against MDR, antibiofilm potential and stability, when it is conjugated in chitosan-based nano particles (Cleophas et al. 2014; Almaaytah et al. 2017). Wu et al. reported the formation of nisin incorporation in nanoparticles by self-assembly of chitosan and poly-gamma-glutamic acid. *In-vitro* antibacterial study of the chitosan-containing composite show potent activity against *E.coli* and *Listeria* monocytogenes compared to nisin/gamma-PGA or nisin alone (Wu et al. 2016). In addition to polymer-based nanoparticles, nanofibrous materials derived from natural or synthetic polymers are promising wound dressing substances based on unique properties like high surface area, porosity, and lower adverse effects (Andreu et al. 2015). Natural and synthetic polymers have exhibited their own merits and demerits (Maftoonazad et al. 2019; Topuz et al. 2021; Hamdan et al. 2021). When compared to natural polymers, synthetic polymers have several advantages such as processability and offer good mechanical properties, for example, Poly (ε-caprolactone) (PCL), poly-lactide (PLA), poly-glycolide (PGA), Polyvinyl alcohol (PVA), etc. (Maftoonazad et al. 2019). Nowadays, researchers focus on a new attractive methodology to enhance the antibacterial efficacy of AMPs coated into biocompatible polymers that extensively combat multi-drug resistance. To improve the physiochemical property of nanofibers, electrospinning technology has been widely used (Mouro et al. 2021; Deng et al. 2018; Mirzaeei et al. 2021). It is a cost-effective approach extensively used in biological and medical practice. Specific nanofibers are generated by applying a strong electric field (Zare et al. 2021). As a result, the electrospun polymeric nanofibers exert special properties like shape, size, and surface interactions. These enhance the therapeutic activity and are utilized as a drug cargo for other natural antibiotics. The unique nature of nanofibers enabled the creation of drug-filled nanofibers with a stable release of drug at the infection site (Pan et al. 2021; Topuz and Uyar 2018; Pankajakshan et al. 2016; Contardi et al. 2017; Ashbaugh et al. 2016; Chen et al. 2014).

Proline-rich peptide APO loaded into PVA (polyvinyl alcohol) nanofibers has been reported as a solid patch dressing application (Sebe et al. 2016). Microgel/nanogels are another type of AMP delivery vehicle. For example, incorporating novicidin into modified hyaluronic acid results in greater encapsulation (up to 70%) and a peptide load above 36%. It has strong stability (colloidal) and exhibited constant peptide release for two weeks (Water et al. 2015). AMP CysHHC10 into a polyethylene glycol (PEG) hydrogel matrix formed on polyethylene terephthalate by thiol-ene reaction resulted in hydrogels with antimicrobial action against gram-positive bacteria (*S. aureus* and *S. epidermidis*). The combination of PVA and

Chitosan recently provided heat resistance for nanofibers to encapsulate gentamicin for curbed release of up to 72 h (Hamdan et al. 2021). Likewise, PEG polymer covalently attached with HHC10 AMPs shows strong resistance against proteolysis and increased activity against MDR pathogens (Almaaytah et al. 2017). Giram et al. reported that fabricated Eudragit L-100 nanofibers encapsulated with Moxifloxacin to accelerate drug delivery. The antibiotic-loaded nanofibers exhibit potent antimicrobial activity against gram-positive *S.aureus* and negative *E.coli* (Giram et al. 2018). Synthetic and natural polymers are used to fabricate nanofibers because of their biocompatibility, processability and biodegradability (Rofeal et al. 2022; Cruz-Maya et al. 2019). Biopolymer-based nanofibrous wound dressing are extensively reliable and easily biodegradable (Parham et al. 2022). On the other hand, the major setback of using natural or designed AMPs could be instability. Hence, it is essential to stabilize the long-acting peptides with the help of biopolymers to retain their stability and multifunctional activity. Nanofibers are widely used as a carriers for curative agents, namely, antibiotics, peptides, and natural extracts. Polyacrylic acid/polyvinyl alcohol nanofibers coated with nisin show superior antimicrobial activity against *S.aureus* up to 14 days (Santiago-Morales et al. 2016).

Polymer multilayers provide a great opportunity for developing surface coatings, capsules, or particles. For instance, poly methacrylic acid (PMAA) and polyvinylpyrrolidone (PVP) encapsulated with cationic peptide L5 by layer-by-layer deposition has been reported to completely inhibit *S. epidermidis* growth (Pavlukhina et al. 2010). Polymer conjugates are the best tool to enhance the activity of peptides, proteins, and drug delivery systems. In this context, further studies are also needed to relate to the importance of antimicrobial effects after pathogen exposure. Additionally, AMP-containing nanoparticle systems remain elusive in nanotoxicology, and AMP drug delivery has the potential for complete fulfilment. Overall, investigations reveal that the utilization of drug cargo promotes the transformation of AMPs from the laboratory research level into clinical trials and further moves forward to a wide range of clinical use.

Antibiotics and AMPs Conjugates for Future Clinical Applications

Antibiotic substances are more efficient against pathogenic microorganisms (Kościuczuk et al. 2012; Moravej et al. 2018). However, due to abuse and excessive use of antibiotics, their efficacy is lost over time, leading to multidrug resistance (Lau et al. 1860). The global expansion of drug-resistant bacteria and the competitive scramble between weak pipelines of innovative antibiotics are the main causes of antimicrobial resistance. The antibiotic crisis is a severe problem that has slowed down all aspects of national growth, including healthcare systems (Lim et al. 2016). Hence, creating new chemical entities requires more effort and resources, and it is particularly difficult to re-isolate old compounds. An innovative and unconventional therapeutic approach can be used to combat AMR. AMPs are short peptides ubiquitous in nature produced by various organisms, including bacteria, fungi, and plants, first discovered in the 1980s. The MOA of AMPs is unique, especially regarding membrane permeability, which is a potential and recognized mechanism compared to conventional antibiotics (Lei et al. 2019). However, natural peptides are not stable, and toxic effects consistently persist. Synthetic AMPs become more stable once chemically modified and maintain their biological activity during unfavourable conditions (Mahlapuu et al. 2016). To extend clinical use, developing strategies and prospects of long-lasting AMPs via chemical modification by conjugating potential antibiotics are necessary to overcome the problems associated with the cell membrane barrier of the superior chemical entities. AMPs are also called as antibiotic adjuvants, or delivery vehicles for other chemical entities (Schafer et al. 2021). Outer cell membrane-penetrating AMPs are synthesized and conjugated to existing small organic molecules to carry biomolecules across cell membranes and deliver various other drugs and compounds (Schafer et al. 2021). Therefore, joined armaments can eliminate AMR more efficiently through various mechanisms of action, especially cell-penetrating and host defence mechanisms (Lei et al. 2019; Lim et al. 2016). Recently, promising broad-spectrum antimicrobial activity has been obtained by conjugating AMPs with D-amino acid residues linked to fatty acids (Zhong et al. 2020). For instance, vancomycin conjugated with arginine enables the influx of vancomycin and inhibits the cell wall synthesis of Gram-negative bacteria (Antonoplis et al. 2019). Thus, the consolidated peptide-antibiotic conjugates approach improves antimicrobial efficacy by adding existing antibiotics to treat antimicrobial resistance- associated infectious diseases.

Conclusion

Genetic changes or mutations can lead to the natural emergence of antimicrobial resistance over time. Pathogens can spread rapidly between individuals, enabling bacteria to evade the effects of existing antibiotics, potentially leading to superbugs. Overcoming these infections is now the most challenging step. The discovery of novel antimicrobials is laborious, expensive, and risky, requiring significant resources. Recently, researchers have focused

on prospective replacements with distinct AMP interfacial actions to increase efficacy against various infections without causing AMR to improve further. However, a significant barrier to stop bacterial infections which remain due to natural peptides' short life and toxicity. To overcome this limitation and create more effective treatment regimens, it is crucial to synthesize and improve AMPs for clinical applications. Dual therapy using small molecule-peptide conjugates is an excellent alternative for defeating against AMR. These combinatorial therapies preserve the unique properties of peptides and enable other small biomolecules to penetrate the outer cell membrane barrier of vital bacterial (gram-negative) infections. By adopting these integrated techniques, activity is improved, and the transition from targeted to broad-spectrum therapeutic actions is accelerated without furthering the emergence of antibiotic resistance. Most importantly, preserving the effectiveness of currently available antibiotics helps addressing issues with nosocomial infections linked to AMR and hospital-acquired infections. Utilizing a combination of AMPs and small molecule conjugates provide a potential strategy to address the threat of drug-resistant superbugs.

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Declarations

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