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Popular Article

Antimicrobial Peptides - An Emerging Alternative

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Abstract

The use of antimicrobials in animals as therapeutic, metaphylactic, prophylactic, and as growth promoter agents had started centuries back to enhance food production. Later on, due to extensive use of these antibacterials had led to emergence of resistance in bacteria. Antimicrobial peptides have received a great amount of attention due to their broad spectrum of antimicrobial activity against various microorganisms such as fungi, viruses, and bacteria in both veterinary and human pathogens, rapid killing activities, less toxicity, and cell selectivity. They are constituted of short-chain amino acids which are amphiphilic, and positively charged which allows them to bind and penetrate the bacterial membrane bilayer to induce pores causing intracellular leakage whereas some AMPs work by targeting intracellular components like inhibition of cell wall, nucleic acid and protein synthesis, and restriction of their enzymatic activity. The antimicrobial aspects of AMPs is that they are effective against multidrug- resistant pathogens, and compared to conventional antibiotics, they kill pathogens extremely fast, using multiple bacterial targets. The tracheal AMP (TAP) has been reported to have bactericidal activity against the pneumonia causing pathogens in cattle, such as *Mannheimia haemolytica*, *Histophilus somni*, and *Pasteurella multocida*. Likewise, many peptides are well known to possess antifungal, antiviral activity and some are proven to be good growth promoters when included in the diet of animals. AMPs account for worldwide research minefield, studies for the detection of new AMPs from various sources are increasingly continuing, as these are unique molecules that are proven to be promising candidates to treat multi drug resistant organisms.

Keywords: Antimicrobial peptides, resistance, antifungal AMPs, antiviral activity

Introduction

Majority of antibiotics being used in contemporary world got discovered in 1940s and 1960s, therefore referred as ‘golden age of antibacterials’. It is the most important and useful discovery in history of medicine. Antimicrobials are utilized as therapeutics, metaphylactic, prophylactic and as

growth promoters. Due to the unselective utilization of antimicrobials for a long time has led to the formation of significant reservoir of microbes with antimicrobial resistance genes. Antibiotics were used to treat the diseased animal, as in many cases as prophylaxis measures. The unfolding and rapid spread of multidrug resistance microbes has become a serious threat to animal health globally because of their less responsiveness to conventional antimicrobial therapy.

In recent decades, antibiotic-resistant bacterial infections are an alarmingly increasing worldwide problem [1]. The urgent need for developing alternative agents to control microbial diseases has been the major driving force in the development of peptide antibiotics, which could become the most potent solution in cases where current antibiotics are insufficient.

Development of Resistance

The mechanisms involved in the development of resistance can be both genetic and environmental. The main mechanism involved in the development of resistance involves- impermeability of outer membrane, production of drug degrading enzymes, various efflux pumps or by altering the targets.

For example, bacteria can become resistant by limiting or reducing the penetrability of their cell envelope against exposed antibiotic or by mutation or disruption of the gene as in the case of *Pseudomonas aeruginosa*, by which they gain resistance to imipenem by losing expression of the porin OprD, which is the transporter for this antibiotic. Alternatively, some of the bacteria degrade the antimicrobials by ß-lactamase production which is a alarming issue due to development of expanded spectrum ß-lactamases (ESBLs) resulting in the emergence of new, nonresponsive bacterial clones [2]. Sometimes by the losing the chemical affinity between an antimicrobial and its target, may also led to resistance as occurred in the case of streptococci and this mechanism was also reported as the chief reason of penicillin resistance in meningococci [3]. Some of researchers have reported that some bacterial cells may have various types of efflux system which is capable of pumping out antimicrobials aiding in development of resistance.

Pathogen acquire this resistance mechanism intrinsically or via horizontal gene transfer or by mutation as consequence of exposure to different drugs. Along with this, indiscriminate use of antibiotics in veterinary medicine, lack of proper regulatory mechanism, improper diagnosis and lack of surveillance and monitoring, all together have put selective pressure for emergence of AMR strains.

So, there are some alternative strategies to combat antimicrobial resistance, which includes- Phytocompounds, in which the bioactive chemical agents are derived from plants, had reported to

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have efficacious antimicrobial activity and can be explored to address antimicrobial resistance, furthermore, there is phage therapy, where some bacteriophages are used to treat bacterial infections.

Antimicrobial peptides (AMPs)

AMPs are also referred as host defense peptides. These are multifunctional peptides that protect animal against infection, being innate in nature they exibit low cytotoxicity to host. They have wide spectrum of biological activity including- eliminating pathogenic microbes gram negative, gram positive, fungi viruses, have low resistance among microbes, enhanced wound healing actions, also participate in regulation of immune system and show anti-inflammatory and anti tumor effects.

Briefly AMPs are small-sized proteins that are crucial elements in host immune defense in most living organisms, including animals, humans, insects, fishes, and plants [4]. They are constituted of short-chain amino acids which are amphiphilic and positively charged which allows them to bind and penetrate the bacterial membrane bilayer to induce pores by “toroidal-pore”, “barrel-stave,” and “carpet”, thus causing intracellular leakage [4].

Mode of action of AMP

The exact mechanism associated with antimicrobial action of AMPs is complicated, as one single peptide can target different sites in the microbe. This activity of AMPs is due to suppression of cell wall, nucleic acid and protein synthesis, and inhibition of enzymatic activity [5]. Several studies have identified that the antimicrobial mechanism of AMPs kills bacteria due to increased membrane permeability, induction of lipid asymmetry, and loss of cellular components and essential metabolites, which ultimately leads to cell death [6]. In addition to membrane permeabilization, AMPs can kill bacterial cells by targeting not only DNA but also the biosynthesis of cell wall, LPS, and other biological pathways [7].

A. Membrane Interaction Mechanisms

AMPs attach to the bacteria cell wall by electrostatic interactions between the anionic component of a membrane and the positive charge of a peptide [5]. After binding, the peptides cross the cell wall and cell membrane to contact the cellular membrane in Gram-positive bacteria. For Gram-negative bacteria, the first action of AMPs involves the competitive displacement of Mg2+ and Ca2+. Then these peptides destabilize this supramolecular assembly and gain access to both inner and outer membranes. Following the attachment, AMPs are inserted into the membrane to form transmembrane pores and are divided into four models: (1) the barrel-stave model in which the peptides penetrate the membrane and form pores in the hydrophilic portion, (2) the carpet model in which the peptides disrupt the membrane structure by a detergent-like action, (3) the toroidal model in which the

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hydrophilic portion of the amphipathic conformation of peptides is associated with the lipid headgroup, and (4) the aggregate model in which the peptide penetrates the membrane and damaging it [5].

B. Targeting Intracellular Components

Besides the membrane damage, the peptide can kill bacteria by restricting the biosynthesis of nucleic acid, proteins, and some essential enzymes from synthesizing cell walls and bacteria growth [5]. AMPs can interfere with key enzymes involved in transcription, translation, and assembly, such as chaperones, leading to inhibition of proteins. For example, pyrrhocoricin targets ribosomes to inhibit protein translation, whereas PR-39 inhibits protein synthesis in *E. coli* by inhibiting the transition from the initial to the extension phase [8].

Furthermore, AMPs can induce degradation of DNA and RNA or affect key enzymes involved in DNA synthesis. For example, indolicidin can target a basic site of DNA to crosslink single- or double-stranded DNA, and it can also inhibit DNA topoisomerase I [9]. Besides inhibiting nucleic acids and proteins, AMPs can inhibit the metabolic activity of cells due to the effect on protease activity.

AMPs have received a great amount of attention due to their broad spectrum of antimicrobial activity against various microorganisms such as fungi, viruses, and bacteria in both veterinary and human pathogens, rapid killing activities, less toxicity, and cell selectivity [10].

Some AMPs tend to work by sequestration of ions vital for bacterial survival. Hepcidin and Psoriasin reduce the concentration of iron and zinc ions, respectively, and thus restrict the growth of pathogens.

Chemical Synthesis of Antimicrobial Peptides

Chemically**,** these peptides can be synthesized in solution phase and in solid phase. In solution phase, firstly, the two amino acids are taken and reagent is added for their bond formation. In this method, along with the peptide of interest we may get undesirable peptides also, so there removal is required prior to addition of third amino acid also this method is limited to synthesis of dipeptides and tripeptides.

In solid phase peptide synthesis, we take Resins, which act as solid support and are inert in nature and have linkers attached to it. In this we take FMOC protected amino acids and their deprotection is done by 20% piperidine. Kasier test is then performed, to determine the amino acid end is free or not. After which washing is done with DMF. After few cycles, when the desired length of peptide is obtained, trifluroacetic acid is added. After 2 hrs of incubation, diethyl ether is added and precipitation of peptide occurs [11].

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Classification of AMPs

AMPs are large and diverse and can basically be divided into major groups based on structure, source, and biological activity [12]. Based on the sources, various peptides are identified in animals, humans, insects, microorganisms, and plants, and based on structure, the AMPs are classified into four categories: α-helix, β-sheet, extended, and loop [13]. On the other hand, based on biological activity, peptides are classified as antibacterial peptides, antifungal peptides, antiviral peptides, antiparasitic peptides, and anticancer peptides [5].

Probing of AMPs in Veterinary Medicine

Antibacterial Peptides

There are two broad classes of AMPs reported in livestock, first is Bovine β-defensins which includes- TAP, LAP, DEFB1, DEFB3, DEFB4, DEFB5 and DEFB10 and second is Cathelicidins which includes- CATHL 1–7, Bactenecins, Indolicidin Bovine and Myeloid Antimicrobial Peptides (BMAPs) [14].

Tracheal AMP (TAP) is the first reported β-defensin. Vulikh *et al.* [15] reported that it has bactericidal activity against pneumonia causing pathogens in cattle, such as *Mannheimia haemolytica*, *Histophilus somni*, and *Pasteurella multocida.*

Lingual Antimicrobial Peptide (LAP) are secreted by epithelial cells from alveoli and mammary glands. Kawai *et al*. [16] concluded that it has efficient bactericidal activity against *E. coli*, *S. aureus and P. aeruginosa.*

Bovine Myeloid Antimicrobial Peptides

Takagi *et al*. [17] reported that bovine myeloid antimicrobial peptides (BMAP- 27, BMAP-28 and BMAP-34) were found to be highly effective against various pathogens of veterinary interest due to their antimicrobial and cytotoxic effect.

In agreement to this, Tomasinsig *et al*. [18] reported that BMAP-27, BMAP-28, Bac5, and indolicidin have broad spectrum of activity against most bacterial isolates from bovine mastitis with MIC in the range of 0.5–32 μM.

Kennel Cough which is a highly contagious respiratory disease of dogs caused by *Bordetella bronchiseptica.* Its distinctive symptoms include- loud, hacking cough along with running nose, snezzing etc.

Erles and Brownlie [19] reported that CBD1036 have antimicrobial activity against the respiratory pathogen *Bordetella bronchiseptica.*

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Certain AMPs have been identified to have activity against another disease of dogs i.e. inflammatory bowel disease which is a type of chronic enteropathy characterized by gastroenteritis due to infiltration of cells such as lymphocytes, plasma cells, eosinophills and macrophages. Nakazawa *et al*. [20] reported that expression of CBD1036 is increased in dogs with inflammatory bowel disease.

Antifungal Peptides

Some peptides are reported to have fungicidal activity like Rautenbach *et al*. [21] have reported that echinocandins showed fungicidal activity against *Candida* spp., which causes sour crop in poultry and fungistatic activity against *Aspergillus* spp., which affects the respiratory system of young birds.

Similarly, Takagi *et al*. [17] have reported that indolicidin (CATHL4) have potent fungicidal activity against *Cryptococcus neoformans*, *Candida albicans* in bovines.

Antiviral Peptides

Jung *et al*. [22] reported that antiviral peptides exert their killing effect by inhibiting virus attachment and virus cell membrane fusion, destroying the virus envelope or by inhibiting virus replication.

Liang *et al*. [23] worked on transmissible gastroenteritis, which is an acute rapidly spreading viral disease of all ages of swine, characterized by diarrhea and vomiting and concluded that bovine antimicrobial peptide-13 inhibits the viral proliferation by disruption of the viral protein synthesis and the viral gene expression of transmissible gastroenteritis virus.

AMPs are reported to have promising results on foot and mouth disease, which is highly contagious disease affecting cloven footed animals caused by aphthovirus characterized by smacking of lips, drooling saliva, blisters like sores on tongue, lips, mouth, teats and between hooves. Huang *et al*. [24] reported that AMP Epi-1 causes the inactivation of virus particles and has potent inhibitory activity against foot-and-mouth disease virus.

Moreover, another viral disease of chicken is infectious bronchitis caused by Corona virus, which is highly contagious infection and characterized by gasping, coughing and nasal discharge and since there is no specific treatment for viral diseases so we can go for exploring these peptides. Some researchers have reported that infectious bronchitis virus (IBV) and the inoculation of swine intestinal AMP (SIAMP)–IBV mixed solution- remarkably reduced the mortality of chicken embryos, showing the good inhibitory activity of SIAMP on IBV.

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Anti-mycobacterial Peptides

Human neutrophil peptides (HNP1-4) which are defensins peptides, are actively present on skin or other epithelial surfaces. These HNPs kill mycobacteria probably by inhibiting the biosynthesis of macromolecules and/or increasing the permeability of the bacterial cell membrane.

Sosa *et al*. [25] used K9CATH peptide in the treatment of experimental pulmonary tuberculosis, identifying that *M. tuberculosis* treated with this peptide showed disruption of the membrane, condensation of the cytoplasmic content and significant decrease in colony forming units (CFU) and pneumonic area.

Anticancer Peptides (ACPs)

Ma *et al*. [26] reported that these peptides exert anti-tumor activity either by recruiting immune cells to kill tumor cells or by inducing the necrosis or apoptosis or by inhibiting angiogenesis to eliminate tumor nutrition and prevent metastasis or by activating certain regulatory functional enzymes.

Pan *et al*. [27] reported that pardaxin, a 33 amino acid peptide, isolated from marine fish has anti-tumor activity and concluded that it has strong therapeutic potential for treating the perianal gland adenomas in dogs.

Antiparasitic Peptides

Progression in the field of AMPs for the treatment of parasitic disease is much complicated task major factors include diversity of parasitic groups, their complex life cycles involving multiple stages in different hosts and their different protein expression and membrane composition.

Plasmodium- First antiprotozoal host defense peptide to be identified was magainin-2, which causes the inhibition of Plasmodium falciparum growth by the hybrid peptide cecropin-melittin (CA 1–13 and H1–13).

Leishmania- Temporins, bombins, magainins, and cathelicidins are some of leishmanicidal peptides [28]. Dermaseptin S4 and its synthetic analogs potently induce the lysis of promastigotes.

Taeniasis and cysticercosis- Temporin A and iseganan IB-367 (a protegrin-1 derivative of the cathelicidins family) have antiparasitic effects against Taenia crassiceps, the causative agent of tapeworm. In *in vitro* tests, these peptides are seen to cause damage in the tegumentary surface of the cysticerci to induce morphological changes.

AMP as Growth Promoters

They have beneficial effects on nutrient digestibility, intestinal morphology and intestinal microflora and thus on growth performance in animals and hence they are also used as growth

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promoters. Many AMPs have the potential to be used in poultry, swine, and ruminants breeding and aquaculture, because- improve production performance, improves immunity and promote intestinal health, have inhibitory effect on bacterial inflammation [29].

Gasco *et al*. [30] have used AMP complex, containing mixture of lactoferrin, cecropin, defensin, and plectasin (2 g and 3 g kg^{-1} feed), which have resultant in improved growth performance, reduced the incidence of diarrhea and increased the survival rate of weaned piglets.

Limitations

Despite of their effective therapeutic use in the treatment of multi drugs resistance microbes antimicrobial peptides also have unwanted traits like toxicity to eukaryotic cells which could result in hemolysis, nephrotoxicity, immunogenicity and neurotoxicity. These are susceptible do proteolysis by bacterial proteases. Their production cost is much higher. They lack appropriate delivery system to the target site. They have undefined pharmacokinetic profile. In addition to this, they are cationic and amphiphilic in nature, which results binding to the serum proteins after parental administration which consequently results in rapid removal from blood circulation and accumulation within reticular endothelial system thus, ensuring in toxic effect and decrease therapeutic activities.

Conclusion

The emergence of multi drugs resistance microbes has prompted the need to develop new strategies to address the problem of drug resistance leading us to antimicrobial peptides which are basic elements of innate immunity. Despite of their role to tackle the spread and emergence of multi drugs resistance microbes, they are prone to proteolytic enzymes and are cytotoxic and lack efficient delivery system and requires high manufacturing cost. To overcome this, interaction of multi-disciplinary subject like biology, material science, chemistry, bioinformatics and pharmacy is at most required. In veterinary medicine, it is necessary to perform more *in vivo* studies that can be correlated with results observed *in vitro.* Antimicrobial peptides constitute global research but many key issues in design and application needed to be solved urgently as these are unique molecules that are proven to be the promising candidate to treat multi drug organisms.

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