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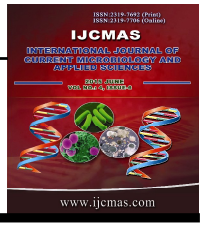

Review Article

Antimicrobial Peptides: The next generation therapeutic agents

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A B S T R A C T

Antibiotics are commonly used in meat industry across the world for treatment, prevention and control of diseases. Besides at low concentration the antibiotics are also used as growth enhancers. Low concentration or subtherapeutic, are given as feed and water additives which improve daily weight gain and feed efficiency through alterations in digestion and disease suppression. Wide spread and some time indiscriminate use of antibiotics has been accompanied by the emergence of microorganism that are resistant to these agents. Antibiotic resistant have been posing increasingly serious concern to the public, health specialist and food animal producers. To overcome antibiotics resistance and to retain consumer confidence in a safe food supply, health specialist and food animal producers are searching for alternative, yet effective means of preventing and treating emerging and re-emerging diseases. Thus, new approaches to the problem of antimicrobial resistance and development of novel classes of antimicrobial agents with less likelihood to gain resistance are needed. Antimicrobial cationic peptides are prevalent throughout nature as part of the intrinsic defenses of most organisms which can act as blueprint for the design of novel antimicrobial agents.

Introduction

The availability of complete genome sequences and development of information technology have provided a greater opportunity for peptide based drug designing. The field of structure based drug designing is a rapidly growing area and the exposition of genomic, proteomic and structural information has provided new targets and opportunities for drug lead discovery.

In the meat industry, the use of antibiotics as growth enhancers is a common practice and extensive use of antibiotic in meat industry causes an alarming increase of antibiotic resistance microbes across the world (Gorbach, 2001). Antibiotic resistance has been posing increasingly serious concern to the public, health specialist and animal food producers.Therefore, there is a need of alternative group of drugs which are active *in vivo* and are able to act fast and has broad-spectrum activity, do not induce bacterial resistance and have limited or no

side effects.Antimicrobial peptides are prevalent throughout the nature as part of the intrinsic defenses of most organisms. These peptides represent ancient host defense molecules and act as key elements in non-specific immunity (Ganz and Lehrer, 1989).Their wide spread distribution throughout the animal and plant kingdoms suggest that antimicrobial peptides have served a fundamental role in the successful evolution of complex multicellular organisms (Bal, 2000). New strategies are required for synthesis of novel antimicrobial agents to deal with the threat of bacterial resistance (Ravi *et al*., 2011). Antimicrobial peptides hold promise as broad-spectrum alternatives to conventional antibiotics (Gee *et al*., 2013).

The rapidly responsive and phylogenetically ancient innate immune system of host defense is generating increasing interest due to its broad spectrum of effectiveness. Epithelial physical and chemical barrier system represents an important part of the innate immune system preventing primary infection as these surfaces are equipped with various antimicrobial substances (Schroder, 1999).The most common sites of initial encounter with microbes are the epithelial lining of the different organ as well as different physiological system. The epithelial layer of the vertebrates provide the first line of defense against pathogens and hostile environment (Jacob and Zasloff, 1994). If this barrier is breached, microorganism invades and an acute inflammatory response occurs (Gallin *et al*., 1988).

The activation and deployment of pathogen specific immune responses occurs slowly relative to the potential kinetics of microbial proliferation and restricted to higher eukaryotes which contain immune cells capable of recognizing antigens and responding with effectors cells. The acquired immune system is primarily cellular in composition, relying on the actions of B and T cells which are not triggered rapidly enough to protect against exposure to any pathogen or infection. But the non-specific innate immune response is more immediate which depends upon the activity of phagocytic cells such as macrophages and neutrophils and in the expression of a number proteins and peptides. The rapidity of the innate immune system provides effective host defense against a vast array of microbes in a manner that is independent of previous exposure to any pathogen.

Specific antigens recognition by lymphocytes plays a limited role during initial encounter by microbes. Epithelial physical and chemical barrier system represents an important part of the innate immune system preventing primary infection as these surfaces are equipped with various antimicrobial substances (Schroder, 1999). These epithelial derived molecules can restrain microbes by causing structural disruption or metabolic injury. The absence of functionally important immune system in lower vertebrates, invertebrates and plants indicates that innate immune system plays vital role to defend them in survival. Peptide based host defense can be considered as a pervasive and evolutionary ancient mechanism of immunity. The innate immunity is very fast and multifunctional in nature (Granz, 2003), and is mediated, at least in part by the potent antimicrobial action of cationic peptides against gram positive and gram negative bacteria, fungi, parasites and even some viruses (Hancock and Lehrer 1998; Brogden *et al*., 2003).

Antimicrobial peptides with broad spectrum activity are widely distributed in nature and have been characterized from plants, insect,

amphibian as well as mammals, including human (Andreu and Rivas, 1998; Bullet *et al*., 1999; Sitaram and Nagaraj, 1999). Multicellular organisms live by and large, harmoniously with microbes. Antimicrobial peptides are distributed ubiquitously in plant, bacteria, insects, amphibian and mammals and by virtue of their broad spectrum antimicrobial activity use to fend off a wide range of microbes including bacteria, fungi and protozoa (Barra and Simmaco, 1995; Steiner *et al*., 1981). Bombinins, magainins and dermaseptins are best characterized group of antimicrobial peptide and has been isolated from amphibians (Simmaco *et al*., 1993; Simmaco *et al*., 1994). Antimicrobial peptides are expressed from those parts of animals that are most likely to come into contact with pathogens from the environment. Thus they are found in skin, epithelial surfaces of tongue, gut, trachea and lungs (Robert *et al*., 2000).

Antimicrobial Peptides have considerable therapeutic potential as these peptides prevents from colonizing and growing to a point where they can cause life threatening infection. As antimicrobial peptides are effective components of host defense, that can be explored as possible alternative to conventional antibiotics. Traditional antibiotics usually have single or limited types of target molecules, which can be mutated easily by bacteria to gain resistance. The action of antimicrobial peptide involve the direct electrostatic interaction with negatively charged microbial cell membrane, followed by physical disruption and capable of killing broad range of microorganism due to lack of involvement of specific receptors (Hancock,1999). These peptide kill micro-organism rapidly compared to conventional antibiotics and appear to be refractory to the development of resistance. All these attributes make them attractive candidates as next generation therapeutic agents for treating multi-drug resistant bacterial infections.

Antimicrobial peptides cover a wide spectrum of gene encoded and ribosomally synthesized molecules from bio-synthetic precursors that display a considerable diversity in size and structure. The primary translation product is generally pre-protein which is processed by definite pathway to pro-protein and processed further to mature active peptides by specific pathways (Bals, 2000). Antimicrobial peptides of various families differ in size, amino acid sequence and certain structural motif. Families of antimicrobial peptides genes are located in clustered, in close proximity on the same chromosome, which suggests that they may have evolved from a common ancestral defense gene by duplication (Liu *et al*., 1997). These antimicrobial peptides represent a unique and quite complex host defense tool and have multiple function (Tomasinsig and Zanetti, 2005).

Mammalian defensins and cathelicidins are the two broad classes of antimicrobial peptides constitute a large family of endogenous peptide antibiotics with broad-spectrum activity against various bacteria, fungi and viruses.

All defensins are polycationic 3.5-4.5 kDa, relatively arginine rich nonglycosylated peptides and are characterized by the presence of six conserved cysteine residues forming three intermolecular disulfide bonds with a compact triple stranded β -sheet structure (Lehrer *et al*., 1991). Based on the positions of six cysteine residues and linkages of the disulfide bonds and overall molecular structure, defensins are divided further into three classes: α -defensin, β-defensin and ϕ defensin. α-defensin are 29-35 residues in length containing three

disulfide bridges in 1-6, 2-4 and 3-5 alignment and reveal a triple stranded β-sheet structure with β-hairpin loop that contains cationic amino acids (Zhang *et al*., 1999).β-defensin are 36-42 residues in length and possesses disulfide alignment at 1-5, 2-4 and 3-6 position (Tang *et al*.,1999). A novel class of defensins also has been isolated and named ϕ -defensin for its circular structure in which cysteine residues linking at 1-6, 2-5 and 3-4 (Tang *et al*., 1999). Many β-defensin are expressed by epithelial cells and keratinocytes. Their expression in nonmyeloid cells may occur constitutively or in response to signal that are generated during infection, inflammation or and tissue repair.

Cathelicidins are mostly synthesized from the bone marrow progenitor cells of mammalian species. Precursors of the cathelicidin family possesses a N-terminal signal peptide of 29-30 amino acids, a pro sequence of approximately 99-114 amino acids which is highly conserved both intra and inter species and the C-terminal region there is substantial heterogenesity which encode mature peptide, containing 12 to 100 amino acids.

Expression of human cathelicidin namely hCAP-18 and LL-37 is reported respectively in the reproductive tract (Malm *et al*., 2000) and skin epithelial cell (Markus *et al*., 2012). Several β-defensin namely, human β-defensin-4 from testis (Garica *et al*., 2001), cryptidin from mouse sertoli cells (Grandjean *et al*., 1997), Bin1b from rat epididymis (Li *et al*., 2001) has been isolated. Antimicrobial peptide gene in the uterine tract has been characterized from *Bubalus bubalis* and the potency of the individual amino acids has been analyzed (Kalita, 2015). On the basis of amino acid sequence of natural antimicrobial peptides various analogues can be prepared by replacing with desired amino acid. Antimicrobial peptide gene from buffalo tongue has been sequenced and characterized (Kalita and Kumar, 2009). Synthesis of different length of natural analogue of buffalo lingual antimicrobial peptide and functional study revealed its potency against both gram positive and negative bacteria (Kalita *et al*., 2009). Designed and synthesized antimicrobial peptides qualifies as prototypes of innovative drugs that can be widely explored as novel antimicrobial drugs to reduce the adverse affect of antibiotic.

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