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Antimicrobial Peptides (AMPs): Roles, Functions and Mechanism of Action

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Abstract

Antimicrobial peptides (AMPs) are a crucial part of innate immunity that exist in the most of living organisms. In fact, AMPs have ability to incite the innate immune response and combat with a broad range of microbes, including bacteria, virus, parasite and fungi. Moreover, recent studies indicated that, the small cationic peptides have ability to target cancer cells and can be used as the cancer therapeutic agents. AMPs are the very tiny macromolecules, commonly in the range of 6 to 100 amino acids. During last decades with the growing antibiotic resistance, AMPs have gained considerable attention because of potential application to combat multidrug-resistant microorganisms. Therefore, herein we aimed to review the features of antibacterial peptides, including their classification, structure, source, mechanism of action and clinical application. Furthermore, problems in the production of recombinant peptides and also newest researches in the clinical developments of AMPs for treatment of crucial diseases; particularly cancers will be reviewed.

Keywords Antimicrobial peptides (AMPs) · Antibiotics resistance · Innate immunity · Cancer therapeutic

Introduction

Several decades ago, peptides have been isolated and purified from bacteria, fungi, algae, insect herbs such as miltinin, morrisin secroupin, ponaretoxin, mastoparan, scorpion, frogs and mammals. The most attention are focused about their features, especially targeting different ion channels and cell membrane components (Hmed et al. 2013). Over than 750 eukaryotic antimicrobial peptides (AMPs) have been reported until now (Hancock et al. 2016) that are collected according to their sequence homology, functional similarities and three-dimensional structure (Payandeh et al. 2019; Peravali et al. 2013). AMPs form the important part of the immune system (Brogden et al. 2016), as the activity of them creates a perturbation in the plasma membrane which causes cell lysis (Peravali et al. 2013). Therefore, it seems that these peptides with spread-spectrum emerge can be as a new potential therapeutic agents (Brogden et al. 2016).

Despite the existence of the majority antibiotics, AMPs seem to act as a safety regulator, enhancing immunity that is the unique properties of these peptides (Li 2011). Considering high biological activity and low cost of the AMPs, they can be considered as a good candidates for drug synthesis by many pharmaceutical researchers (Hurdle et al. 2011;

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Midura-Nowaczek and Markowska 2014). In this review, we first give an introduction of antibacterial peptides, and then discuss about their source, structure and mechanism of action. In the following, we focus on the problems of recombinant peptides production and finally, we consider the recent researches in clinical developments of AMPs for treatment of important diseases; particularly cancers.

Classification of Antibacterial Peptides

The peptides from scorpion sources are classified into two main groups including non-disulfide-bridged peptides (NDBPs) with multiple activity (Table 1) (Almaaytah and Albalas 2014; Zhang et al. 2015) and peptides with disulfide bridges. The NDBPs can be divided into two subgroups consisting of cationic peptides and acidic peptides. The number of amino acids are varied from 13 to 56 (Santibáñez-López and Possani 2015). As regards, the high biological activities of these peptides such as lysis feature, anticancer effect, immune regulatory function, bradykinin-potentiating factor and significant antimicrobial activity lead to study about NDBPs (Ramírez-Carreto et al. 2015). The peptides with disulfide bridges usually target the membrane boundaries of ion channels. They were applied in the treatment of diseases such as epilepsy, glioma, autoimmune diseases, neurological diseases and chronic pain (Pahlavan et al. 2019; Zhang et al. 2015). The majority of these peptides are classified into four different subgroup based on targeting ion channels (Hmed et al. 2013) and used as the modulatory agent or blocking activity of the ion channels (Santibáñez-López and Possani 2015). Recently reports indicated that fungi as the widespread family of eukaryotes can produce peptides with antimicrobial properties (Table 2). They are a new generation of antibiotics which can be a good alternative of new biological molecules. Many of these have anti-tumor activity and can cause the mortality of many cancer cells by prevention of their growing with less detectable mechanisms. Diphencin is a group of peptides that are responsible for protecting the host. The similarity in structure of fungal AMPs involves the discontinuity of β-plates which stabilized by disulfide bonds however, α helix observed in some homelands of these peptides (Kastin 2013). Antifungal peptides are another type of peptides which are often produced by filamentary fungi. They are very small and rich in cysteine for producing three or four disulfide bridges. Some of antifungal peptides isolated from the fungi and fungi sensitive to these peptides are listed in Table 3. These peptides are often made in the form of adult prephenate peptides so they are inactive and protected in the host (Sathoff et al. 2019; Shah 2019).

Another classification of antibacterial peptides are based on the structure of their amino acids (Hmed et al. 2013). Antibacterial peptides are usually between 12 and 50 amino acids in length (Huang et al. 2010) containing positively charged amino acids, such as arginine, lysine or histidine which provide an acidic environments along with 50% of hydrophobic area (Mojsoska et al. 2015). Moreover, antibacterial peptides can be classified into two another categories including; synthetic non-ribosomal peptides and synthetic ribosomal peptides or natural (Keymanesh et al. 2009; Zheng et al. 2017). The first group mostly is produced by bacteria while the latter one is produced by all animals and bacteria (Martin et al. 2017).

Ultimately, electrostatic charge is as an important feature for classification of AMPs (Moreno-Montoro et al. 2017). According to this characteristic, the antibacterial peptides are divided into two major categories. A large number of peptides are cationic peptide having positive charge while the other groups include non-cationic peptides (Ashby et al. 2017) which are scarce. Interestingly, in the scientific literature, the "antibacterial peptides" term only refers to its cationic type (Sudheendra et al. 2015).

Structure of Antibacterial Peptides

The structure of antibacterial peptides are in four styles, including α-helices, β-sheet, extended and loop forms (Fig. 1) (Narayana and Chen 2015; Nguyen et al. 2011). Natural derived antibacterial peptide divided into peptides with β-sheet, α-helix, cyclic peptides and peptides with long lengths. β-Sheet and α-helix are more abundant in nature (Harmouche et al. 2017a). Most of linear antibacterial peptides lose their structure in solution, while cyclic peptide form β-sheets due to the presence of one or more disulfide bond 'cysteine-cysteine' (Teixeira et al. 2012). The most of AMPs have less than 100 amino acid residue that are essential for antimicrobial activity (Fjell et al. 2012). Hydrophobic property such as α-helices, β-sheets and polyprolin helices are increased during the formation of secondary structure (Khurshid et al. 2016; Poluri and Gulati 2017).

Action Mechanism of Antibacterial Peptides

AMP's mechanism is dependent on the number of physicochemical properties including the sequence of amino acids, charge, amphipathic property, structure especially secondary structure, and etc. (Mojsoska et al. 2015). These peptides have different mechanisms for disrupting the membrane (Mahlapuu et al. 2016). Despite of having suitable characteristics of AMPs (Bayer et al. 2017), many researchers believe that the ability of AMPs for binding to membranes of bacteria has an important role in the development of them (Bayer et al. 2017; Juretić et al. 2017). Some mechanisms of binding AMPs to membranes of bacteria include

Table 1 List of non-disulfide-bridged peptides (NDBPs) of scorpion venom with number of amino acids, biological function and its scorpion species (Akef 2019; Almaaytah and Albalas 2014; Cid-Uribe et al. 2018; Doğan et al. 2018; Uzair et al. 2018)

NDBPs	Number of amino acids	Biological activities	Scorpion species
Peptide T	13	Bradykinin-potentiating	*Tityus serrulatus*
K 12	21	Bradykinin-potentiating	*Buthus occitanus*
Hadrurin	41	Antimicrobial, hemolytic	*Hadrurus aztecus*
Pandinin 1	44	Antimicrobial, hemolytic	*Pandinus imperator*
Pandinin 2	24	Antimicrobial, hemolytic	*Pandinus imperator*
Opistoporin 1	44	Antimicrobial, immune-modulatory, hemolytic	*Opistophthalmus carinatus*
BmKb1	18	Antimicrobial	*Mesobuthus martensii*
BmKn2	13	Antimicrobial, hemolytic	*Mesobuthus martensii*
IsCT	13	Antimicrobial, hemolytic	*Opisthacanthus madagascariensis*
IsCT2	13	Antimicrobial, hemolytic	*Opisthacanthus madagascariensis*
Parabutoporin	45	Antimicrobial, immune-modulatory, hemolytic	*Parabuthus schlechteri*
Mucroporin	17	Antimicrobial	*Lychas mucronatus*
Meucin-13	13	Antimicrobial, hemolytic, cytolytic	*Mesobuthus eupeus*
Meucin-18	18	Antimicrobial, hemolytic, cytolytic	*Mesobuthus eupeus*
Imcroporin	17	Antimicrobial, hemolytic, cytolytic	*Isometrus maculates*
StCT1	14	Antimicrobial, hemolytic	*Scorpiops tibetanus*
Meucin-24	24	Antimalarial	*Mesobuthus eupeus*
Meucin-25	25	Antimalarial	*Mesobuthus eupeus*
Im-1	56	Antimicrobial, hemolytic, cytolytic	*Isometrus maculatus*
HP 1090	13	Antiviral	*Heterometrus petersii*
Vejovine	47	Antimicrobial, hemolytic	*Vaejovis mexicanus*
Ctriporin	19	Antimicrobial	*Chaerilus tricostatus*
BmKbpp	47	Antimicrobial, hemolytic, bradykinin-potentiating	*Mesobuthus martensii*
VmCT1	13	Antimicrobial, hemolytic	*Vaejovis mexicanus*
VmCT2	13	Antimicrobial, hemolytic	*Vaejovis mexicanus*
AamAP1	18	Antimicrobial, hemolytic	*Androctonus amoreuxi*
AamAP2	18	Antimicrobial, hemolytic	*Androctonus amoreuxi*
StCT2	14	Antimicrobial	*Scorpiops tibetanus*
HsAP	29	Antimicrobial, hemolytic	*Heterometrus spinifer*
Css54	25	Antimicrobial, hemolytic	*Centruroides suffusus suffuses*
UyCT1	14	Antimicrobial, hemolytic	*Urodacus yaschenkoi*
UyCT2	13	Antimicrobial, hemolytic	*Urodacus yaschenkoi*
UyCT3	13	Antimicrobial, hemolytic	*Urodacus yaschenkoi*
UyCT5	13	Antimicrobial, hemolytic	*Urodacus ya schenkoi*
Pantinin-1	14	Antimicrobial, hemolytic	*Pandinus imperator*
Pantinin-2	13	Antimicrobial, hemolytic	*Pandinus imperator*
Pantinin-3	13	Antimicrobial, hemolytic	*Pandinus imperator*
Mauriporin	48	Anticancer	*Androctonus mauritanicus*
TsAP-1	17	Antimicrobial, anticancer	*Tityus serrulatus*
TsAP-2	17	Antimicrobial, hemolytic, anticancer	*Tityus serrulatus*

barrel-stave, toroidal pore worm hole, carpet and detergent like model as shown in Fig. 2 (Kumar et al. 2018). In the barrel-stave model, peptides with a special direction are placed between membrane and joined together to form an ion channel (Harder and Schröder 2016; Krauson 2011). In the toroidal pore worm hole model, peptides are placed in parallel direction with double layer membrane. In this orientation, spiral hydrophilic head is placed toward hydrophilic region of lipids and the aqueous phase is outside of membrane while hydrophobic head is placed in the hydrophobic center of membrane (Gaspar and Castanho 2016) and finally, in the carpet model, peptides mounted on the

Table 2 A list of antimicrobial fungal diphenins with the number of amino acids and their sources (Kolyada 2019; Ma et al. 2019; Manchisi et al. 2019; Medeiros-Silva et al. 2019)

Antimicrobial peptides	Number of amino acids	Source of AMPs	Antibacterial activity against
Plectasin	95	*Pseudoplectania nigrella*	Gram-positive bacteria: *Streptococcus* spp., *Staphylococcus* spp., *Enterococcus* spp., *Corynebacterium* spp., *Bacillus* spp.
Eurocin	90	*Eurotium amstelodami*	Gram-positive bacteria
Micasin	38	*Microsporum canis*	Gram-positive and gram-negative bacteria: *B. megaterium*, *B. subtilis*, *Staphylococcus* spp., *M. luteus*, *B. cereus*, *P. aeruginosa*, *A. tumefaciens*, *E. coli*
Copsin	184	*Coprinopsis cinerea*	Gram-positive bacteria: *B. subtilis*, *Streptococcus* spp., *Staphylococcus* spp., *Listeria* spp., *Enterococcus* spp., *Micrococcus luteus* spp.

Table 3 A list of antifungal peptides isolated from the fungi with the number of amino acids and their sources and fungi sensitive to these peptides (Alex et al. 2019; Babič et al. 2019; Kovács et al. 2019; Richmond-Rakerd et al. 2019; Shishodia et al. 2019)

Antimicrobial peptides	Number of amino acids	Source of AMPs	Activity against sensitive fungi
Antifungal protein	51	*Aspergillus gigenteus*	*F. oxysporum*, *F. moniliforme*, *F. graminearum*, *F. poae*, *F. sporotrichoides*, *B. cinerea*, *E. graminis*, *M. grisea*, *P. infestans*, *P. recondita*, *S. graminicola*
PAF (*Penicillium* antifungal peptide)	55	*Penicillium chrysogenum*	*B. cinerea*, *F. oxysporum*, *F. sambucinum*, *C. carbonum*, *T. koningii*, *A. flavus*, *P. graminis*, *P. recondite*, *A. fumigatus*
NAF		*Penicillium nalgiovense*	
AcAFP (*Aspergillus clavatus* antifungal protein)	94	*Aspergillus clavatus*	*F. oxysporum*, *F. solani*, *B. cinerea*, *A. solani*, *A. niger*, *A. solani*
BP (bubble protein)	184	*Penicillium brevicompactum*	*S. cerevisiae*
NFAP (*Neosartorya fischeri* antifungal protein)	57	*Neosartorya fischeri*	*F. graminearum*, *Mucor* sp., *A. flavus*, *Byssochlamys* sp., *F. solani*, *Geotrichum candidum*, *P. roqueforti*, *P. italicum*, *P. digitatum*
AnAFP (*Aspergillus niger* antifungal protein)	58	*Aspergillus niger*	*A. flavus*, *A. fumigatus*, *F. oxysporum*, *F. solani*, *Candida albicans*
PgAFP	58	*Penicillium nalgiovense*	*A. flavus*

membrane surface to create disorder and chaos (Harder and Schröder 2016). Accumulation of peptides in an appropriate concentration increases the curvature of the membrane which leads to increase formation of membrane spiral pores (Gaspar and Castanho 2016; Wang et al. 2016). In this mechanism, peptides cover the carpet, forming membrane surface that resemble to early stages of a "spiral hole" (Iglic and Kulkarni 2014). It works like a detergent and breaks membrane into the small pieces (Lohner 2017). After this step, peptides aggregate together and increase local concentration. According to their amphipathic property, pieces are like micelles (Andreev et al. 2016; Lohner 2017).

Moreover, the other insertion models of host defense peptide such as molecular electroporation and sinking raft model are shown in Fig. 3 (Bechinger 2011). In the sinking raft and molecular electroporation models unstable holes are formed in membrane, changing the electric charge on the two sides of the membrane and ultimately develops holes (Miao et al. 2015). Plant and mammalian membranes such as red blood cells membrane consist of neutral phospholipids and large amounts of cholesterol while, bacterial cell membranes is rich of acidic phospholipids such as phosphatidylglycerol and cardiolipin (Kornspan and Rottem 2012). Electrostatic interaction between negatively charged phospholipids and positively charged AMP's as well negative bacterial membranes is a major driving force for cellular communication (Huang et al. 2014; Paiva and Breukink 2013). Figure 4 shows the outer parts of the plant and mammalian membranes has no charge, because the negatively charged membranes lipids are on the inner surface of the plasma membrane. In fact, the outer surface of the membrane usually was made from phosphatidylcholine and sphingomyelin with a small portion of some ganglioside (Hemler et al. 1995) so, the

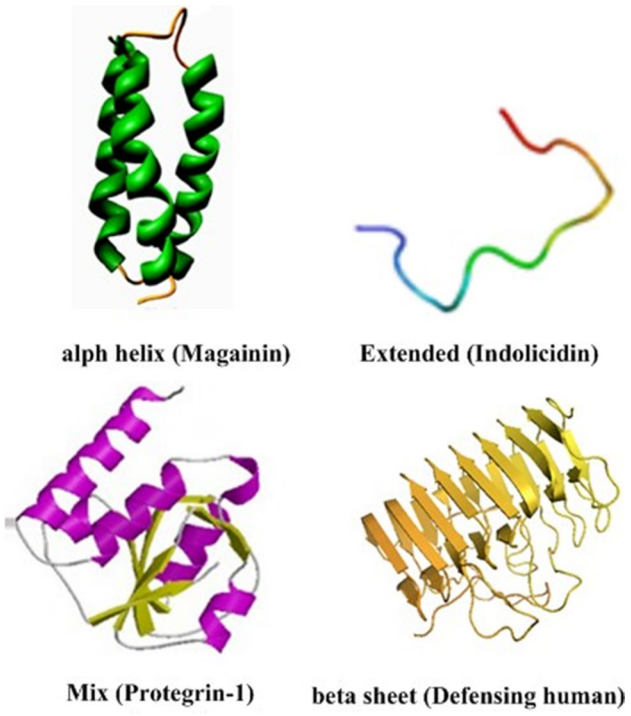

Fig. 1 Structures type of antimicrobial peptides

interaction between amphipathic AMPs with the plant and mammalian membranes are very week. While the effective interaction is present between the hydrophobic part of amphipathic AMPs and the outer parts of bacteria membranes due to existence of negative charge phospholipids (Del Vecchio and Stahelin 2018).

Sources of Antibacterial Peptides

Antibacterial peptides are synthesized by most organisms including bacteria, fungi, algae, plants, insects (*Melittin*, *Moricin*, *Cecropin*, *Poneratoxin*, *Mastoparan*) frogs and mammals (Ingber et al. 2013). Animal AMPs were first discovered in invertebrates and later found in vertebrates. These peptides have shown different sequences, structures and goals (Li et al. 2012). Toxins from animals and plants are natural resources and rich in biological molecules (de la Salud Bea et al. 2015). AMPs also are obtained from milk peptides (Dziuba and Dziuba 2014; Théolier et al. 2014). In addition to natural resources, these peptides can be produced synthetically (Fjell et al. 2012). Since, hitherto synthetic peptides have made and sold commercially (Uhlig et al. 2014). AMPs are produced by four chemical methods, including culture of industrial microorganisms, genetically modified organisms, enzymatic hydrolysis of proteins and separation from natural sources. With protein engineering, the discovered species are also continuously improving. Compared to separation protocol of natural sources and chemical synthesis, it can be suggested that recombinant methods to be better method in regard to production scale through profitable methods (Li 2011).

Recombinant Antibacterial Peptides

AMPs are one of the compounds commonly used instead of antibiotics, displaying pathogenic bacterial resistance. These protein-like molecules often contain some depleted or modified amino acids that are not found in polypeptides made by

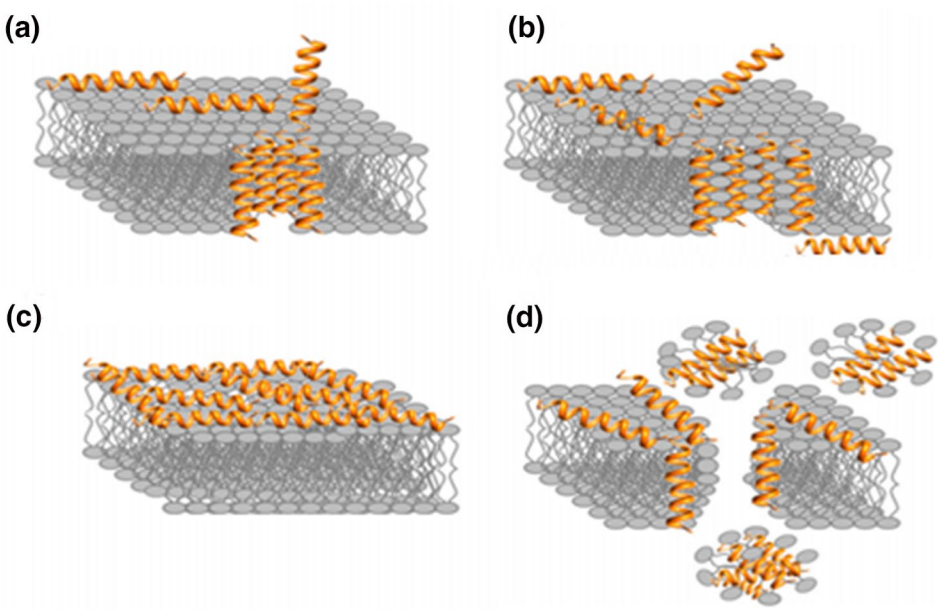

Fig. 2 The mechanism of peptides activity in bacteria. **a** The barrel-stave model. **b** The toroidal-pore model. **c** The carpet model. **d** Detergent "like" model (Kumar et al. 2018)

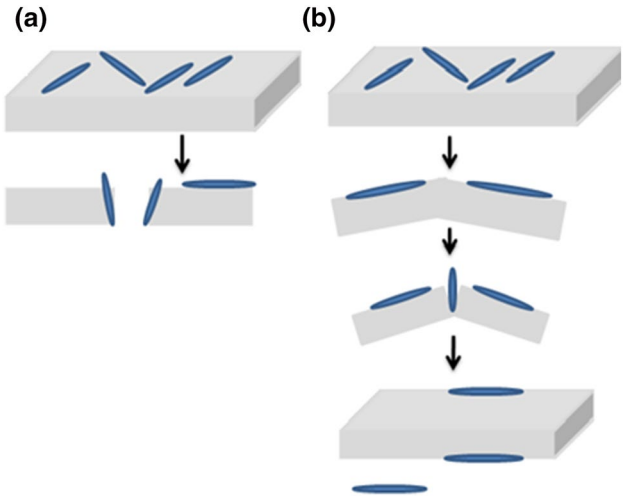

Fig. 3 Host defense peptide membrane insertion models. **a** Molecular electroporation model and **b** sinking raft model (Bechinger 2011; Mander and Liu 2010)

ribosomes (Bondaryk et al. 2017). Based on their biosynthesis mechanism, these compounds classified in two groups consist of bacteriosins and peptide antibiotics. Bacteriosins are ribosomal synthesized compounds which produce by bacteria and act against the other close kinship bacteria. Unlike Bacteriosins, the second group of recombined AMPs are synthesized by stepwise and compression reactions which associated by non-ribosome peptide syntheses (NPRS; Thoendel et al. 2010). The main obstacle in the use of antibacterial peptides, as antibiotics, is their ability to lyse eukaryotic cells especially red blood cells. Indeed, for application of them, they should have low hemolytic activity and have high antimicrobial activity. Recent studies have shown that the high hydrophobicity and amphipathic property of AMPs to associate with hemolytic activity (Wang et al. 2015). Therefore, the range of selection of these peptides should be improved to lower hemolysis or other toxicity, in this case, modification of current methods for designing or identifying of AMPs can be helpful to achieve these goals. In order to apply AMPs in therapeutic application, production of small AMPs by recombinant DNA methods is a challenge approach to discuss. *Escherichia coli* (*E. coli*) is the most commonly used host for expressing AMPs due to high growth rate. However, some problems such as low crop yields, proteolytic decomposition of the hybrid protein and toxicity of the expressed product on the host should be considered about AMPs (Li et al. 2017). Various ways are presented for overcoming these problems, for instance use of hybridization, production of expression vectors containing multiple linked genes or addition of anionic fragment to counteract and neutralize the cationic peptides. Positive AMPs are loaded with acidic components that can be neutralized and significantly reduce their toxicity effects on host cells. Bioreactor studies have been identified that production of antibiotics is strongly dependent on the scale of work and more importantly, is related with dissolved oxygen concentration, pH environment, glucose consumption and cell differentiation. These peptides are now mainly produced from extraction of host organisms or in solid-phase peptide synthesis (SPPS). SPPS has become the dominant method for peptide production (Mehrlatifan et al. 2016; Yazdani et al. 2019). However, both of them are expensive and produce

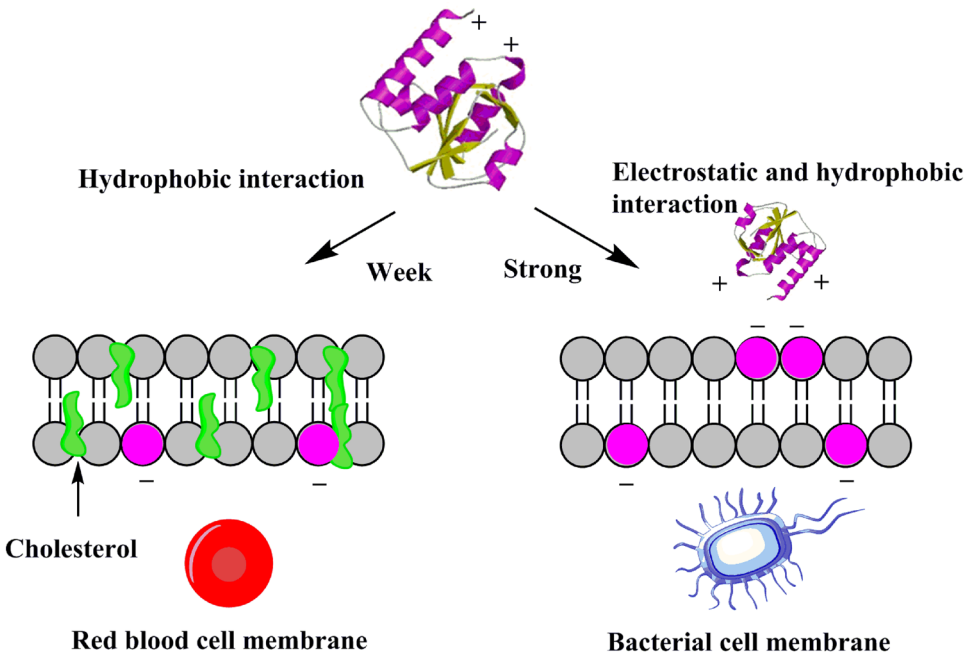

Fig. 4 Molecular basis of cell selectivity of antimicrobial peptides in plant and mammalian in comparison with bacterial cells (Gerner and Raffatellu 2018)

low yield. It seems the recombinant DNA technology is useful for production of various prokaryotic and eukaryotic proteins (Gaglione et al. 2019). In fact, the recombinant DNA technology has opened a new window for production of these compounds cheaper than the previous systems. For a long time, *E. coli* strains are a good host for heterologous proteins production. In general, the bacterial peptides can be produced easily in the cytoplasm of the bacterium. Multiple host-carrier systems have been used to produce AMPs via recombinant DNA technology using *E. coli* (Baird 2017). One of the major problems when working with peptides is to obtain sufficient materials with determined structural and functional properties (Mehrlatifan et al. 2016). This problem becomes harder when they combined with peptides rich in disulfide bonds, as they may produce non-native disulfide-bond isoforms. For example, a peptide with 3 disulfide bonds can be 15 and 1 peptide with 4 disulfide bonds can form 105 different disulfide isomers, respectively. There are several methods for expressing cytoplasm in *E. coli* to produce peptides rich in disulfide bands. One way to overcome this problem is bypassing the cytoplasm which secretes the recombinant protein to the bacterial periplasm where the endogenous protein forms a disulfide bond. The recombinant peptides with an annual growth of 15%, account for a large amount of market for pharmaceutical products. The combination of recombinant DNA technology and mass production process, makes it possible to commercially produce them (Harrison et al. 2015; Uhlig et al. 2014). Over the past several years, extensive research has been conducted on the production of multiple recombinant peptides including human growth hormone, interferon gamma, GM-CSF, G-CSF, interleukin-2, streptokinase, and etc. Although, a lot of peptides have been introduced as novel drugs however, their high flexibility cause limitation for application of them as antibacterial drugs. Peptides are hydrophilic compounds so they cannot cross the brain barrier. In addition, the short-lived half-lives and high cost of formulation are another disadvantage in comparison with the other novel drugs (Abarghooi et al. 2012). The production system of *E. coli* has several benefits, including rapid proliferation rate, presence of various strains of bacteria, existence of highly expressed genetic systems for the production of alien peptides, development of fermentation methods, proper genetic stability and low mutation rates in the genome. However, there are some problems such as; high levels of endotoxin, insoluble intracellular masses due to high expression speeds that need to be rearranged, lack of post-translational reforming systems (glycosylation, ending amines, sulfation, etc.), degradation alien peptide by cell proteases, lack of disulfide bonds in bacterial cytoplasm resuscitation and so on (Dehaghani et al. 2010; Ebrahimi et al. 2010; Jafari et al. 2014; Mohtashami and Ashtiani 2010; Morowvat et al. 2014a). Extremely high expression of the recombinant peptide in the cell, leads to accumulation of them in an abnormal structure. Creation of ankylosing spondylitis is one of the major problems in production of peptide as a cytoplasmic form (Babaeipour et al. 2008; Bakhtiari et al. 2014; Kahaki et al. 2014; Morowvat et al. 2014b). The expression of heterologous genes is influenced by several factors including stability and copy number of plasmid, promoter power, mRNA stability, ribosomal availability, the efficiency of transcription and translational processes, post translational modifications, stability and solubility of recombinant protein and culture conditions (Cao et al. 2017; Umenhoffer et al. 2017). In addition of *E. coli*, many antibacterial peptides have been expressed in various expression systems (Table 4). In all systems, hydrodynamic condition of immersion fermentation can be improved by changing and modifying the bioreactor structure with an emphasis on aeration optimization and agitation systems (Gaur et al. 2017; Jones et al. 2016; Jossen et al. 2017; Maghsoudi et al. 2009; Morowvat et al. 2015; Oikonomopoulos et al. 2015; Ranjbari et al. 2015). For the first time, Conde et al. (2000) isolated a new peptide was known as scorpin from the scorpion venom. This peptide has an antimicrobial activity and contains 75 amino acids. They found that scorpin has a unique amino acid sequence in which the amino terminus has similarity some of the zirconine and its carboxyl terminus is similar to some diffusers (Conde et al. 2000). Moreover, the gene of scorpion was cloned from a cDNA library. *Ev37* is the first known gene in the Euscorpiidae family which has encoded as the new scorpin pseudo-peptide codon and cloned from the cDNA library of the scorpion venom. *Ev37* peptide contains 78 amino acids. Recombinant peptide *Ev37* and two peptides (*Ev37-N* and *Ev37-C*) in *E. coli* were used for functional studies (Feng et al. 2013; Maghsoudi et al. 2009; Mohseni et al. 2009; Saleh et al. 2008). Although, the use of recombinant AMPs very limited because of the uncontrolled genetic alterations which make through random mutagenesis. However, it appears recombinant AMPs can be promising candidates in the heterologous production in bacteria and other organisms as a cost-effective method.

Application of Antibacterial Peptides

AMPs or host defense peptides have been used in different fields such as therapeutic applications, agriculture, aquaculture, food industry and etc. (Meng et al. 2010). These peptides have several biological activities such as anticancer, immune-modulatory, anti-parasitic, antiviral, anti-biofilm, anti-inflammatory, angiogenesis and wound healing activities (Hilchie et al. 2019). Cancer as one of the main causes of morbidity and mortality in the world which become as a serious health concern for both developed and developing countries (Beaglehole et al. 2011; Siegel et al. 2013).

Table 4 Produced antibacterial peptides from various hosts with number of amino acids, biological function and their references

Peptides	Numberofaminoacid	Expression vector	Solubility	Host	Activity against	References
Lactoferricin	25	pET-21d	Solution	BL21(DE3)	*E. coli*	Arias et al. (2016)
CM4	35	pET32a	Solution	BL21(DE3)	Bacteria, fungi andtumor cells	Li et al. (2017)
Hepcidin	25	pET28a	Insoluble	BL21(DE3)	*Saccharomycescerevisiae*	Kautz et al. (2016)
F4	152	pGNX2	Solution	HMS174(DE3)	Bacteria and *E. coli*	Oudart et al. (2015)
BuforinII	21	pET21c	Insoluble	BL21(DE3)	*Bacillus subtilis*	Chen et al. (2018)
HβD41	36	pET-EI	Solution	BLR(DE3)	*P. aeruginosa*	Prens and Deckers (2015)
CM4	35	pET-EI	Solution	BLR(DE3)	*E. coli*	Chen et al. (2015)
SMAP-29	160	PBlueScriptII	Solution	ER2566	Fungus and bacteria	Jacob et al. (2016)
β-Defensin 2	41	pET-28a	Semi solution	BL21(DE3)	Bacteria	Chang et al. (2017)
Cg-Def	43	pET-28a	Insoluble	Rosetta(DE3)	*Subtilis aureus*,*Escherichia coli*	Rajanbabu et al. (2015)
CruFc	117	PCRT7/NT-TOPO	Semi solution	BL21(DE3)	*Staphylococcusaureus*, *Bacillus subtilis*,*Micrococcus luteus*,*Bacillus cereus*, *E. coli*	Zhang et al. (2018)
DEFA1	34	pET-30-Xa/LIC	Insoluble	BL21(DE3)	*Staphylococcusaureus*, *Bacillus cereus*, *Enterobacter aerogenes*	Chen et al. (2019)
Bin1b	47	pET-28a	Semi solution	BL21(DE3)	Bacterias	Zhou et al. (2015)
MiAMP1	102	pBSV-8His	Not mentioned	BL21(DE3)	Bacterias	Hulett and Lay (2017)
I-TevI	245	pET-28a	Not mentioned	BL21(DE3)pLysS	Bacterias	Roy et al. (2016)

Despite dramatic improvements in the treatment of cancer, resistance to anti-cancer drugs remains a major problem, leading to efforts in development of novel anti-cancer agents with new performance (Cardoso et al. 2018). Although it is not clear why some host defense peptides are capable of destroy cancer cells while the others do not (Fakheri and Jabbari 2014; Huang et al. 2015; Wang 2014). Electrostatic attraction between the cationic peptides and cell membrane anionic components is the most important factor in selective function of AMPs (Harder and Schröder 2016; Sadredinamin et al. 2016). Due to increased expression of anionic molecules, cancer cells membrane contain negative charges, so it can be assumed that these peptides may destroy cancer cells (Polyansky et al. 2010). Cationic AMPs are one of the most prominent classes of membrane active peptides. These peptides have a potential as a cancer inhibitory effect and cause biomembrane lysis (Araste et al. 2018). Amphipathic AMPs destroy membrane integrity, leading to membrane leakage and death of cancer cells which mediated by the hydrophobic and electrostatic interactions (Guo et al. 2016). Positive net charge of AMPs (+4 to+6) causes to interact with the negatively charged phosphate head groups of cancer cell membrane and hydrophobic region. Some of AMPs have dual activity, including as an antimicrobial agent and as a selective anticancer peptides (ACPs) by lytic activities against membrane, however some of them penetrate inside cells and act on intracellular targets (Sani and Separovic 2016). Multiple α-helical ACPs display an anticancer activity via necrosis and apoptosis mechanism (Huang et al. 2015). Polybia-MPI, Temporin-1CEa, LTX-302, Anoplin, Cecropin A/ B and A12L/A20L exhibit specific anticancer activity against various cancer cells and disrupt the cell membrane, leading to necrosis of cancer cells. Mellitin from honey bee venom with specific activity causes disruption of cells with necrosis mechanism (Huang et al. 2015). LL-37, HPRP-A1, Pardaxin, BMAP-28 and RGD-tachyplesin can induce apoptosis in some of cancer cells. Magainin II (MG2) and A9K have anticancer activity by several different mechanisms of action (Huang et al. 2015). Cecropin B has a potential anticancer activity against leukemia cells, stomach cancer, and lung cancer. A novel modified peptide CB1a as an ACP derived from cecropin B showed apoptosis activity in leukemia and carcinoma cells (Qin et al. 2019). Several amphibian AMPs such as magainins, aureins, tryptophyllins, dermaseptins, phylloseptins, bombinins (BLP-7) and bombinin (H-BO) showed antiproliferative activity (Zhou et al. 2018). Furthermore, some peptides like bacteriocin have the cytotoxicity activity against various human cancer cells. Bacteriocin enterocin-B and the heterodimer of bacteriocins (enterocin-A + B) as antibacterial agents have the growth inhibitory effect of against HeLa, HT-29, AGS, Caco2 and MCF-7 cancer cells (Ankaiah et al. 2018). Antiproliferative activity of some plant-derived antimicrobial polypeptides was assayed against some of cancerous cells lines like Hela, Bt-549 and Neuro-2a. These peptides showed significant cytotoxicity with the highest IC_{50} against

Neuro-2a (Al Saiqali et al. 2018). Another possible inducing cause of planned death in cancer cells is arrival of AMPs in the cytoplasm, causing turbulence in the mitochondrial membrane (Chen et al. 2015).

Assessment of commercial development of AMPs in different countries were shown utilization of peptide drugs in various stages of treatment such as catching an infection, diabetic foot ulcers, acne, mucus membrane infections, gingivitis and meningitis (Rzepiela et al. 2010; Strandberg et al. 2009). Furthermore, one of the most important advantages of these peptides as drugs is that they have no side effects (Tieleman 2017; Woo and Wallqvist 2011). Since peptides are natural substrates that can stick to a large number of enzymes and receptors, it seems that their utilization in drug synthesis can be a successful approach. However, for usage of these peptides as a medicine, manipulation of these compounds particularly in their properties such as metabolic stability, high tendency and specificity for a particular enzyme or receptor should be considered (Harmouche et al. 2017b). Other usage of these peptides is application in agriculture which includes control of post-harvest corrupt and insect as plant pests. Regarding the control of post-harvest corruption, the use of chemical fungicides has become increasingly restricted due to resistance to them (Vetchinkina et al. 2016). In the case of aquaculture, the use of vaccines and antibiotics in the aquatic environment has increased concern about the occurrence of resistance, so using AMPs is a good solution for overcoming this problem. Another application of these peptides is in the food industry. Indeed, adding preservatives is the usual way to prevent or reduce microbial growth in food products, so AMPs are a good choice as preservatives. Among these peptides, the bacteriocin is the most prominent group due to effectiveness against gram-positive bacteria, the main cause of food poisoning (Stern Bauer and Hayouka 2018). Multi-functional activities of AMPs, including antibacterial, antiviral, anti-fungal, anti-parasitic and protease properties have led researchers to pay attention to the application of them in the food industry, agriculture and medicine sciences in recent years.

Conclusion

AMPs are an important component of innate host defense which have anti-microbial, anti-viral, anti-cancer and contraceptive activities. They can be a good alternative to antibiotics and chemical preservatives. These peptides contain different chemical structures, sequences and transcripts, having antimicrobial activity. In the near future, it is expected to witness significant progress in using AMPs instead of antibiotics. On the other hand, a large number of AMPs not be used properly. Therefore, more efforts are needed to examine the applications of these compounds, especially in the new sectors of food and medicine. For example, there is an increasing awareness of the role of AMPs in reducing the incidence of certain cancers, especially clonal cancer. The exact mechanism of this phenomenon is not identified, it is probably due to control of mutagenic compounds by direct binding to carcinogens or inhibition of microbes that produce these agents. Therefore, there is a high potential for use of AMPs and further research is in demand to have significant effects in the food and medicine industry.

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