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A Review Of Biological Properties Of Bioactive Peptides: Antimicrobial Activity

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Abstract: *Bioactive peptides are specific fragments of proteins, the activity of which is based on the composition and sequence of amino acids. Nowadays, various sources and methods are used to obtain these peptides. The microbial fermentation and enzymatic hydrolysis or a combination of both are commonly employed to obtain bioactive peptides. However, in some instances, other methods such as ultra-filtration or chromatography may be used to obtain the peptides due to the presence of the desired peptide in an intricate complex. Bioactive peptides can be of plant or animal origins. The bacteriocins are among bioactive peptides with antimicrobial activity, which can be of bacterial origin. These types of bioactive peptides increase the permeability through binding to the bacterial wall and perforate the wall, thus exhibiting their antimicrobial activity. The three models, including barrel stave models, the toroidal model, and the carpet model, are the most common mechanisms of action of antimicrobial peptides. Antimicrobial peptides can be used to treat human, animal, and plant diseases caused by microorganisms. They can also be applied as food preservatives and act as a resistance factor against spoilage caused by microorganisms. Although some of these peptides have been commercialized so far, extensive and commercial use of them requires further research and experiments.*

Keywords— Antimicrobial; Bioactive peptide; Biological properties; Food; Preservative

1. INTRODUCTION

There are many natural ingredients in foods that assist in preventing diseases, slow down the progression of diseases, and even treat the diseases. These properties of natural ingredients originate from existing proteins and peptides and make these foods to be known as medicinal foods. In recent years, the attention of researchers has been paid to bioactive peptides and their properties due to the high cost of production and, ultimately, the high cost of synthetic and chemical drugs for consumers. In addition to the high cost of production, the side effects of synthetic drugs are considerably high and may deteriorate the patients' condition due to their physical weakness. Bioactive peptides are defined as peptide sequences within proteins that can have positive effects on body performance or and human health beyond their known nutritional value [1,2]. Bioactive peptides can be prepared by proteolytic hydrolysis or during food processing such as baking, Ripening or fermenting processes. Bioactive peptides typically contain 3-20 amino acids, and the sequence strength and composition of these amino acids determine their biological activity [3].

1.1 Extraction and Obtaining the Bioactive Peptides

The microbial fermentation and enzymatic hydrolysis or a combination of both are commonly employed to obtain bioactive peptides. The biological function of bioactive peptides is more appropriate compared to their parent protein; hence, these peptides are released and extracted using some laboratory methods. After identifying the protein source, specific and non-specific proteases can be used to release the desired peptides. Many factors, such as the conditions of the hydrolysis process, the degree of protein hydrolysis, the time of hydrolysis, the type of enzyme, and the size of the desired peptide affect this process. There are two major obstacles to the industrial production of peptides by enzymatic hydrolysis method. The first obstacle is the presence of these peptides in an intricated complex with amino acids, oligopeptides, fibers, and other compounds. The dependence of the bioactive activity of these peptides on some of their physicochemical properties, such as electrical charge, is another obstacle to the production of peptides by enzymatic hydrolysis method; therefore, the development of plant peptides requires methods such as ultra-filtration or chromatography for purification and filtration [4]. During the extraction by fermentation, the lactic acid bacteria are used to release bioactive peptides. Also, proteolytic enzymes isolated from these lactic acid bacteria can be used in enzymatic hydrolysis method. Furthermore, the fungi such as *Aspergillus* can also be used along with bacteria to produce these peptides during fermentation. Three basic mechanisms create the function of the proteolytic system of these bacteria. The activity of several proteolytic enzymes in the cell wall causes the decomposition of proteins into the peptides with the number of 4 to 30 amino acids. Then, there is a transition system that includes binding proteins and two permeases to form a transport channel and two ATPases to provide system energy, and a group of

intracellular peptidases works together for the decomposition of peptides transmitted to amino acids [5].

1.2 Diversity of Antimicrobial Bioactive Peptides

The diversity of antimicrobial peptides is considerably high that has made it challenging to categorize them, and a general classification is applied based on their substructure. The basic structural approach that is the basis of all classes demonstrates the capability of the molecule in the amphipathic selection that the clusters of hydrophobic and cationic amino acids are placed in separated parts of the molecule. The linear peptides are such as the silkworm cecropin [6] and the Manganin of African clawed frog (scientific name: *Xenopus laevis*) [7]. This arrangement is made only after entering the membrane, and then the secondary structure of the alpha helical amphipathic is accepted [8]. The peptides such as Bactenecin [9] and Defensins [10] are relatively stiff non-parallel β-sheets that are encapsulated by disulfide bonds and surrounded by cationic and hydrophobia fragments. A large family of linear peptides characterized by the dominance of one or two amino acids (e.g., Tryptophan-rich Indolicidin in bovine Neutrophils and Proline-Arginine-rich PR39 in porcine neutrophils) [11,12], detaches the hydrophobic and hydrophilic side chains in the surrounding of peptide scaffolds in the membrane. A combination of multiple peptides containing several structural groups is often expressed in defense tissues of multicellular organisms. The changes that occur after translation include proteolytic processing and in some cases glycosylation (non-enzymatic addition of sugar to amino groups of the protein) [13], the amidation of terminal carboxyl and isomerization of amino acid [14], and halogenation (the incorporation of X-ions into organic compounds) [15]. Some peptides are derived from larger proteins such as Buforin II from Histone 2A [16] and Lactoferricin from Lactoferrin by the proteolysis process [17]. Due to the high diversity of sequences, it is rarely possible to find a similar peptide sequence from two different species of animals, even the species of frogs, insects, or mammals (there are exceptions such as peptides isolated from highly protected proteins, e.g., buforin II). However, significant protection of the amino acid sequence in precursor molecules can be identified between specific classes of different peptides of different species as well as in antimicrobial peptides of a particular species [18]. This feature indicates the limitations in the sequences that exist in translation, secretion or intracellular transition, and membrane-degradation peptide groups. The Cathelicidins have significantly shown this feature [19]. What is the reason for this diversity? The single mutations can dramatically cause diversity by altering the bioactivity of each peptide. The adaptation of species to particular microbial environments existed in their habitat (such as microbes related to food sources) is probably due to this diversity [18, 20]. It is normal that a particular species of a living organism to be exposed to the microbes with ineffective peptides over time. They can cause such casualties, but it can cope with microbes and survive microbial agents through the emergence of people who had useful mutations. Since the acquisitive immune system is flexible, this system can discover new environments by a species and use new and more food resources. However, acquisitive immune factors spend more time on maintaining and reducing the time of response to an attack compared to equipment of intrinsic immune systems (such as antimicrobial peptides). The most important features of the acquisitive immune system include specific response to the pathogen and antigen, delayed contact and maximum response, post-exposure immunological memory (thus activated in vaccination of this system), and it can be found only in vertebrates. However, in the intrinsic immune system, the response is non-specific, and without immunological memory, the contact is immediately led to a maximum response, and it is found in all animals [20]. Due to the variety developed in the synthetic laboratory, it can be said that approximately all active molecules consist of hydrophilic, hydrophobic and cationic amino acids arranged in a single molecule that can be organized into an amphipathic molecule [21]. The natural peptides are composed of D-amino acids instead of L-amino acids because the isomers of D-amino acids resist the protease enzymes while fully maintaining the antibiotic properties of the peptides [21]. The rapid digestion of antimicrobial peptides by proteases in the blood flow and cells is one of the major challenges in all of these peptides, which can also be a significant obstacle to using them as effective medicines. The proteases simply decompose the peptide bonds. Reshaping and substituting D-amino acids with L-amino acids is a straightforward way to increase the stability of peptides. Short linear or amphiphilic annular peptides, which contain both L- and D-amino acids, have the potential to be produced with different degrees of selectivity and antimicrobial activity [22,23]. Recently, an antioxidant-resistant antibacterial peptide has been produced, which are composed of β-amino acids [24,25].

2. The Mechanism of Action of Antimicrobial Peptides

An extensive range of methods and tools have been applied to study the mechanism of action of antimicrobial peptides. There is not only a single technique to determine and formulate the mechanism of action of antimicrobial peptides. The placement of the polar heads of phospholipids on the membrane of the cell and the load distribution on the peptides are important factors in the reaction of the peptide with the membrane. In prokaryotic cells (bacterial cells), hydrophilic antimicrobial peptides recognize the anionic lipids on the outer surface of the bacterial membrane.

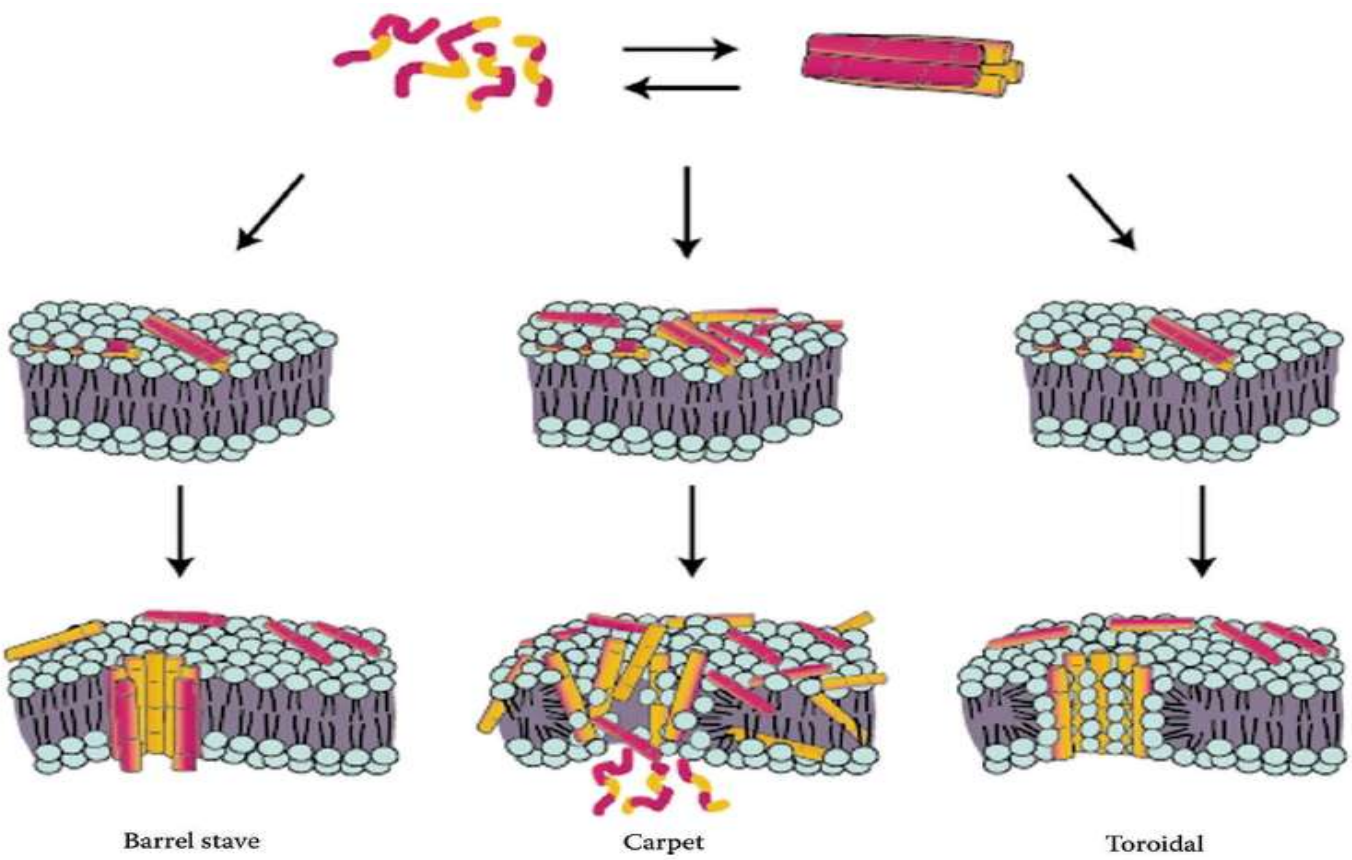

Fig.1. *The potential mechanisms of actions for the antimicrobial activity of bioactive peptides [31]*

In eukaryotic cells, these anionic lipids are placed on the cytoplasmic side of the membrane; this structural feature is a reason for the relatively higher cell killing activity of antimicrobial peptides against bacterial cells than against eukaryotic cells [26]. The death of a bacterium is caused by the formation of pores in the bacterial membrane by three processes of binding the antimicrobial peptides to the bacterial membrane, accumulation of antimicrobial peptides within the membrane, and formation of pores for perforation and killing of cell. Several models explain the increase in membrane permeability through the action of antimicrobial peptides.

Three well-known models are considered as potential mechanisms of antimicrobial action of bioactive peptides: barrel stave, toroidal model, and carpet model [26,27,28].

2.1 Barrel stave Model:

According to this model, antimicrobial peptides are accumulated after binding with bacterial membrane and form dimers and multimers. A barrier-like structure is formed on the bacterial membrane by the accumulation of these peptides. These multimers form some pores in two layers of the bacterial membrane and ultimately lead to cell death [29].

2.2 Toroidal Model:

The path of pore formation in this model is similar to the barrel stave model. The connection of the outer and inner layers of lipids with the peptide toward the two layers of the peptide is a distinct feature of this model. The model is used for most antimicrobial peptides, e.g., Melittin [29].

2.3 Carpet Model:

In this model, the peptides first cover the outer surface of the membrane in a carpet-like pattern and then act as a detergent and lipid bilayers are degraded after the

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concentration of these peptides reaches the threshold. The pores are filled with micelle-like units [30].

3. APPLICATION OF ANTIMICROBAL PEPTIDES

Due to the growing problem of resistance against conventional antibiotics and the need for new antibiotics,

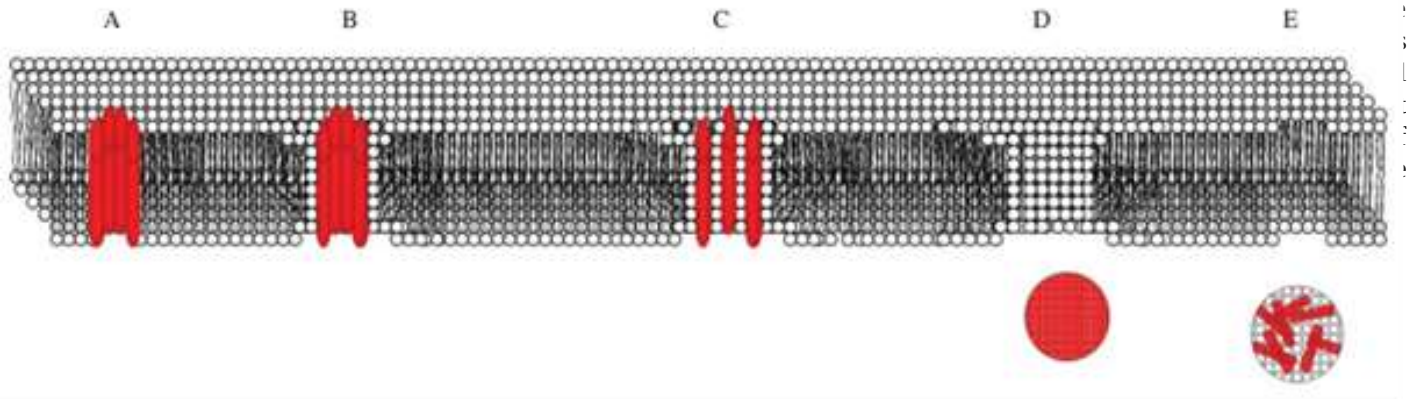

Fig.2. *The models for pore formation by antimicrobial peptides [32]*

Other models related to the performance of antimicrobial peptide include antibacterial properties of many antimicrobial peptides due to pore formation in lipid bilayers. Barrel-stave (A), wedge (B), pore toroidal (C), carpet (D), and aggregate channel (E) models are also referred to as pore-forming mechanisms by antimicrobial peptides (Figure 2) [32]. However, other mechanisms of action of antimicrobial peptides have been described. In the molecular electroporation model, peptides can produce an excellent electrostatic potential for pore formation. In the Sinkingfloat model, the equilibrium in lipid bilayers is impaired after the peptide infiltrates. Such peptides can form temporary pores that are pernicious to bacteria. Defensins and catalysidines can inactivate bacterial lipopolysaccharides by binding to a specific part of the molecule. Many peptides act by inhibiting the processes inside the cell of the microorganism. In the joiningCanal model, the transfer of peptides between lipid bilayers is performed without pore formation. DNA synthesis, protein biosynthesis, or both processes are inhibited by some peptides [27].

The factors that prevent the growth of antimicrobial peptides as systemic therapy are that they are active laboratory conditions but only act at considerably high doses in animal infection models, which is usually close to toxic doses of the peptide and reflects an unacceptable margin of the immune [35]. Antimicrobial peptides have different applications as antiseptic agents. An extensive range of antibiotics originating from antimicrobial peptides is used as "chemical condoms" to prevent the transmission of sexually transmitted diseases such as Neisseria, Chlamydia, HIV, and Herpes simplex virus [36]. Antimicrobial peptides are used in radiotherapy to detect bacterial and fungal infections from sterile inflammation, given the specific binding of antimicrobial peptides to the membrane of pathogens [37]. Antimicrobial peptides are probably capable of enhancing the ability of in vitro antibiotics by facilitating the access of antibiotics into the bacterial cell, a phenomenon previously known for the polymyxin cationic peptide molecule [38]. One of the major concerns in the use of medical devices such as intravenous catheters is the microbial contamination of the surfaces of synthetic polymeric materials. Many pieces of research have been carried out to design novel approaches to prevent microbial contamination and understand the mechanism of absorption and microbial proliferation on the surfaces of materials. The antibiotic binding is an effective, safe, and cost-effective method to reduce the contamination of intravascular catheters in ICU. The use of antimicrobial peptides such as meganine in polymeric materials of these devices through covalent bonding is one of the successful approaches in this regard [39]. One of the important capabilities of some insect-derived antimicrobial peptides is the control of several plant pathogens; it has been proved

that they can be effective through transgenic plants. The expression of transgenic genes from antimicrobial peptides, especially insect-derived antimicrobial peptides, may lead to effective strategies in plants to cope with pathogens for protecting current plants [41,40].

not endanger the health of consumers [48,49]. Pediocin and nisin are the only bacteriocins that are commercially available nowadays. Nisin is used in the dairy industry to increase milk storage time in tropical countries as well as in canned products to eliminate pathogenic bacteria.

Table 1: Some bioactive peptides with antimicrobial activity [51]

LRLKKYKVPQL	Lysine- Arginine- Lysine- Lysine- Lysine- Tyrosine- Lysine- Valine- Proline- Glutamine- Leucine	Interacts with bacteria to cause inhibition
PGTAVFK	Proline- Glycine- Threonine- Alanine- Valine- Phenylalanine- Lysine	Causes bacteria and yeast membrane destruction
KVGIN KVAGT VRT PGDL LPMH EKF IRL	Lysine- Valine- Glycine- Isoleucine- Asparagine Lysine- Valine- Alanine- Glycine- Threonine Valine- Arginine- Threonine Proline- Glycine- Aspartic acid- Leucine Leucine- Proline- Methionine- Histidine Glutamic acid- Lysine- Phenylalanine Isoleucine- Arginine- Leucine	Inhibits Listeria ivanovii and *Escherichia coli* growth
Lp-Def1	L. pisonis defensin 1	Interacts with and impairs mitochondrial functions in *Candida albicans* .
Maize α-hairpinins	-	Binds to microbial DNA to cause cell death

3.1 Application of Bioactive Peptides with Antimicrobial Activity in Food Safety

The ways to prevent or slow down the microbial growth in foods and ultimately to prevent food spoilage are adding synthetic preservatives, such as salts of benzoic acid, sorbates, and nitrites. The limitations of the impact on all pathogens, the lack of effective and safe preservatives, and the tendency of consumers toward purchasing products with minimal processing are among the challenges of using synthetic preservatives [42]. For these reasons, carrying out research to find alternative synthetic preservatives seems to be essential [43]. In the meantime, antibacterial peptides, especially the bacteriocin group, are excellent options [44]. Bacteriocins are ribosomal synthesized bioactive peptide compounds in the form of peptide complexes or released on the extracellular surface that have a bacteriostatic effect on other species. The use of bacteriocins as biological preservatives began about two decades ago [45, 46]. These protein metabolites typically have molecular weights below 10 kDa [47]. For the use of bacteriocins as QPS (Qualified Presumption of Safety), they should be heat-resistant and effective against pathogenic and food spoiler bacteria and to

pproval from the U.S. Food and Drug Administration (FDA) and is employed as a food preservative in many countries [49,50]. Pediocin is also used to maintain safety and increase the storage time of cheese, salads, and meats [52]. Table 1 lists the peptide sequences of some bioactive peptides with antimicrobial activity and their functions.

4. CONCLUSION

The bioactive peptides can be identified as specific amino acid sequences that have beneficial physiological effects. They are actually protein components that are inactive within the protein structure and exhibit different physiological functions when released by hydrolysis. The effects of these peptides include antihypertensive, antimicrobial, anticoagulant, antioxidant, bone protection, and growth enhancement effects, which are different depending on the type and amino acid sequences of peptides. The side effects of synthetic antimicrobial preservatives, as well as antibiotics, have attracted researchers' attention to bioactive peptides with antimicrobial activity, and many studies have been carried out in this regard. However, lack of stable and scalable methods for producing bioactive peptides from different food or non-

food sources, inadequate knowledge of gastrointestinal stability, or peptide absorption by them, and lack of applicable clinical trials to provide basic evidence for potential health claims are among the reasons for the delay in commercialization and the practical applications of these peptides, despite conducting many pieces of research in this field. In general, it can be hoped that the use of active peptides of various properties, especially peptides with antimicrobial activities as substitutes for chemical preservatives in foods to be achievable in the near future with the help of researches being carried out worldwide.

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