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Antimicrobial peptides and their importance in aquaculture

Poulin Shohreh[1], Sedigheh Mohammadzadeh[2*], Rahem Khoshbakht[3]

[1] Department of Clinical Science, Faculty of Veterinary Medicine, Amol University of Special Modern Technologies, Amol, Iran.
[2] Department of Clinical Science, Faculty of Veterinary Medicine, Amol University of Special Modern Technologies, Amol, Iran.
[3] Department of Pathobiology, Faculty of Veterinary Medicine, Amol University of Special Modern Technologies, Amol, Iran.
(*) Corresponding author: Mohammadzadeh.sedigheh123@gmail.com

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Abstract

Intensive fish culture plays an essential role in fish health. The high fish density and unfavourable conditions of water quality factors are potential sources of stress in fish, which often predispose fish to diseases. Infected fish are usually treated using antibiotics, which are not always effective, and the accumulation of these compounds in fish meat endangers the consumers' health. In addition, the excessive use of antibiotics has caused the emergence of antibiotic-resistant pathogens which accounts for a major financial threat to the aquaculture industry. Fish antimicrobial peptides (AMPs) can potentially replace conventional commercial antibiotics in the aquaculture industry due to a wide range of antimicrobial activity, potential of boosting the immune system, and activity at different temperatures and salinities. Therefore, introducing new antimicrobial compounds to treat fish diseases can greatly contribute to the aquaculture industry.

Introduction

Currently, aquaculture is the fastest-growing food supply sector worldwide, which significantly contributes to nutrition and food security, particularly in deprived areas, and it supports the livelihoods of several million people on the globe (Dawood, 2021). The demand for fish has increased primarily because of the rapid population growth and the income from fish culture. High-quality proteins obtained from aquaculture products have made the aquaculture industry the largest activity in the food industry, with an annual growth of 8% (FAO, 2022). However, the expansion of the aquaculture industry faces several major challenges, including broodstock reproduction in captivity, larval culture, and suitable diet preparation, boosting the immune system, and counteracting various diseases. Farming conditions in intensive aquaculture play an important role in fish health. High density of fish, unfavorable conditions of water quality factors, transportation, and vaccination are potential sources of stress in fish that often predispose fish to diseases (Casadei, 2011). Depending on animal husbandry and organizational conditions, the grading of aqueous environments and the spread of bacteriological diseases may reduce production by about 30-40% in aquaculture facilities (Yilmaz *et al.,* 2022). For an extended period, antibiotics have frequently been employed in the aquaculture sector not only for the purpose to avert and/or manage infectious ailments triggered by bacterial pathogens but also as enhancers of growth (Dawood *et al.,* 2018). In addition, the excessive use of antibiotics for disease treatment causes the emergence of antibiotic-resistant pathogens. These pathogens cause the spread of infectious diseases that are difficult to control. Public awareness of the prophylactic use of antibiotics in aquaculture, which may result in the immune transfer of pathogenic bacterial species to humans, has prohibited their use in aquaculture (Dawood *et al.,* 2015).

AMPs are small (up to 50 amino acids residues) and play a role in the innate immune system of various organisms, including mollusks, crustaceans, and vertebrates. These small peptides are generally cationic; hence they can interfere with the bacterial wall to destroy them (Douglas, 2012). These peptides have been changed along with the evolution of pathogens to be able to defend the body against all types of microbes. Therefore, they prevent the generation of mutated pathogen strains resistant to antimicrobial compounds (Douglas, 2012; Katzenback, 2015). Besides, these peptides stimulate the host's immune system and even immune cell attraction to the infection site (Brown and Hancock, 2012; Douglas, 2012). There is no report of pathogen resistance to AMPs, and therefore the peptides can be used as a suitable alternative for antibiotics in medicine and veterinary medicine (Katzenback, 2015; Garvey, 2023). This review focused on the introduction, sources, structure, and most widely and recently used of AMPs in aquaculture.

Antimicrobial peptides

AMPs are peptides with a molecular weight of < 10 kDa (usually containing < 40 amino acids), amphipathic (with two hydrophilic and hydrophobic heads), and generally cationic, which are synthesized ribosomally (Douglas, 2012). AMPs are classified in two forms based on their secondary structure and amino acid sequence. In terms of their amino acid sequence, they can be divided into two main groups: cationic AMPs and non-cationic AMPs (Powers and Hancock, 2003). Based on the secondary structure, these compounds are divided into α-helical, β-sheet, spherical structure, and spatial structure (Reinhardt, 2017). Peptides of the -helical class are characterized by their -helical conformation, and often contain a slight bend in the center of the molecule. Most AMPs are short-length peptides, with amphipathic properties and net positive charge, as well as a multitude of hydrophobic amino acids, belonging to the α-helical subgroup of AMPs (Powers and Hancock, 2003). The β-sheet subgroup is usually characterized by two or more disulfide bonds that maintain their structure like protegrin (Nguyen *et al.,* 2011). The third subgroup, spherical structure, contains large amounts of amino acids arginine, tryptophan, and proline in their sequences (Frank *et al.,* 1990). The fourth subgroup, spatial structure are consisting of human plectacin and human beta-defensin-2. These compounds are non-toxic to the host, can target pathogen structures, and possess a wide range of antimicrobial activity (Valero *et al.,* 2020). Their high diversity in terms of structure and function indicates that they consist of new therapeutic agents that can be used not only in aquaculture but also in human and veterinary medicine (Heuer *et al.,* 2009).

Sources of AMPs

AMPs were first extracted from bacteria, which produce these peptides to kill other microbes in competition for space, food, and other nutrients (Willey and Donk, 2007). However, the widespread identification of AMPs began in the 1960s with the discovery of a peptide with AMPs in polymorphonuclear leukocytes (Zeya and Spitznagel, 1963). The search for AMPs in invertebrates was initiated in 1980 (Steiner, 1982), and then, thousands of AMPs have been extracted and reported from a wide range of organisms. Invertebrates and marine fish mainly depend on the innate immune system to prevent microbial pathogens, thus numerous AMPs have evolved to fight diseases. Marine AMPs have been reported from sponges, marsupials, crustaceans, mollusks, tunicates, and bony fishes (Tincu and Taylor, 2004; Sathyan, 2015). More than 90 AMPs have so far been identified in fish, which are classified into five families, including hepcidin, cathelicidin, β-defensin, peptides derived from histones, and piscidin existing exclusively in fish, based on their structures (Katzenback, 2015). As with other species, peptides produced by fish have a wide range of antimicrobial activity *in vivo* and *in vitro* conditions and can destroy both fish and human pathogens. In addition to antimicrobial properties, piscidins possess antitumor activity (Masso-Silva and Diamond, 2014).

Mechanism of action of AMPs

AMPs are host defense molecules that protect the host against invading pathogens. The action of host defense AMPs can be divided into two different mechanisms: peptides that can directly kill bacteria (Direct lethality) or may act as immune system boosters (Hancock and Sahl, 2006; Steinstraesser *et al.,* 2011).

Direct lethality

Host- defense AMPs are active against Gram-positive and Gram-negative bacteria (Brogden *et al.,* 2003; Reddy *et al.,* 2004). Additionally, these peptides are effective against *Mycobacteria*, which are similar to gram-positive bacteria but have thicker and more hydrophobic cell walls rich in myacolic acids (Miyakawa *et al.,* 1996). While AMPs destroy gram-positive and gram-negative bacteria through membrane disruption, *Mycobacteria tuberculosis* is destroyed through neutrophil phagocytosis, a process facilitated by AMPs that adhere to the surface of these bacteria (Ramon Garcia *et al.,* 2013). Positively charged amino acids in the structure of AMPs facilitate binding to the anionic bacterial cell membrane (Matsuzaki, 1999). Gram-negative bacteria contain lipopolysaccharide as part of the outer membrane, which has a strong negative charge due to the presence of sulfuric acid in their structures and communicates with teichoic acids, lipoteichoic acids, or lysyl phosphatidyl glycerol present in the bacterial wall through interaction with cationic amino acids in AMPs (Lai and Gallo, 2009). AMPs do not harm the body's eukaryotic cells, a reason of which is that eukaryotic cells contain cholesterol, while these compounds are absent in bacterial cell membranes (Lai and Gallo, 2009). Another reason is that eukaryotic cell membranes contain hydrophobic phospholipids that cannot interact with AMPs (Lai and Gallo, 2009).

There are three main models for bacterial membrane rupture by AMPs. One of these models is the Barrel-Stave model, in which the hydrophobic part of the peptide aligns with the acyl chains of the membrane lipids. In contrast, the hydrophilic part of the peptide forms an inner layer that creates channels within the bacterial membrane (Vilcinskas and Wiesner, 2010). Another model is the toroidal-pore mechanism, in which the peptides attach to the head groups of lipids throughout their length, even when they lie vertically inside the membrane. In formatting a toroidal pore, the polar surfaces of peptides interact with the lipid head groups. The peptide and the peptide head group together form a pore so that the lipid monolayer bends along the pore and thereby forms a toroidal pore (Brogden *et al.,* 2003). In the carpet model, peptides lie parallel on the bacterial membrane due to electrostatic interaction between cationic peptides and anionic phospholipid head groups. Local accumulation of peptides leads to membrane disruption and the formation of peptide-lipid aggregates.

AMPs are proposed to have intracellular targets in addition to extracellular membrane disruption. It has been suggested that some AMPs can inhibit cell wall synthesis, alter bacterial cytoplasmic membranes (Yeaman and Yount, 2003), bind to DNA, inhibit protein synthesis, or inhibit the activity of various enzymes (Brogden, 2005). Additionally, AMPs can disrupt cell organelles (e.g. mitochondria) in fungal pathogens and induce cell death (Yeaman and Yount, 2005). Briefly, the exact mechanism of action of AMPs is not known, although these peptides may use multiple mechanisms to induce bacterial cell death.

Boosting the immune system

In addition to the direct killing of microorganisms, AMPs possess the property of indirectly boosting the body's immune system. These peptides can change mammalian cell membranes and stimulate receptors that accelerate intracellular processes (Lai and Gallo, 2009). Furthermore, it has been proposed that host defense molecules can act as chemokines or stimulate the production of chemokines and produce T-cell regulatory cytokines and dendritic cells of the acquired immune system (Lai and Gallo, 2009). In addition, AMPs can influence and accelerate the wound-healing process (Heilborn *et al.,* 2003).

Studies on aquaculture species

Several studies have investigated the identification, sequencing, and introduction of AMPs in different fish species. Moreover, the synthetic and recombinant production of these peptides has been studied in different expression hosts to examine their antimicrobial power against bacteria, fungi, and viruses. The antimicrobial property of the synthesized peptide hepcidin from the sole (*Paralichthys olivaceus*) was evaluated *in vitro* and *in vivo* (Hirono *et al.,* 2005). This peptide showed antimicrobial activity against gram-negative bacteria *Escherichia coli* and *Pasteurella damselae* and gram-positive bacteria *Staphylococcus aureus*, *Lactococcus garvieae*, and *Streptococcus iniae*. Lauth *et al.* (2005) presented evidence that hepcidin synthesized from the hybrid fish (*Morone chrysops* × *Morone saxatilis*) exhibited antimicrobial activity against *E. coli*, *Yersinia enterocolitica*, and *Aspergillus niger*.

AMPs are of paramount importance in fish and human environments. Antibiotic resistance is increasingly on the rise, which leads to the need for AMPs derived from natural sources. Apart from the antimicrobial nature of these peptides, they can be used as anti-neuropathic, analgesic, anti-endotoxic, and anesthetic compounds. In addition, there is a need for research on their design for a large-scale therapeutic approach as these peptides play various functional roles in humans and aquaculture organisms.

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Conflict of Interest

The authors do not have any potential conflict of interest to declare.

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