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Piscidin, Fish Antimicrobial Peptide: Structure, Classification, Properties, Mechanism, Gene Regulation and Therapeutical Importance

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Abstract
Antimicrobial peptides (AMPs) are short molecules produced by almost all organisms. Fish AMPs contain innate immune components as their primary immune molecules. The fish AMPs include piscidins, hepcidins, defensins, cathelicidins and histone-derived peptides. Piscidin is potent and broad-spectrum; this peptide was conserved among Acanthopterygii superorder and is therapeutically important among other AMPs. It was present mainly in the tissues of gills, muscle, head-kidney, skin and intestine of teleost. Piscidin AMP family includes piscidin, moronecidin, pleurocidin, epinecidin, gaduscidin, misgurin, dicentracin, chrysophsin and myxinidin. This review reports the structural properties of various piscidin and their mode of action as it is important to know their mechanism how the peptide involved in antimicrobial activity. In addition, the gene expression of piscidin which influenced the immune responses, their pharmaceutical importance and biological applications were described. Overall, the review explains a broad spectrum of knowledge on piscidin, its classes and types, structure, cytotoxicity, membrane permeabilization, properties and therapeutical implications.

Keywords Piscidin · Fish antimicrobial peptide · Structure · Gene expression · Mode of action

Abbreviations

AMPs	Antimicrobial peptides (AMPs)
AMPPs	Antimicrobial peptides and proteins
SGIV	Singapore grouper iridovirus
VNNV	Viral nervous necrosis virus
MHC	Major histocompatibility complex
TLR	Toll-like receptor
EST	Expressed sequence tag (EST)
LPS	Lipo poly saccharide
NMR	Nuclear magnetic resonance
DPC	Dodecyl phosphocholine
DMPC	1,2-Dimyristoyl-*sn*-glycero-3-phosphatidylcholine
DMPG	1,2-Dimyristoyl-*sn*-glycero-3-phosphatidylglycerol
POPE	1-Palmitoyl-2-oleoyl-*sn*-glycerophosphatidylethanolamine
POPG	1-Palmitoyl-2-oleoyl-*sn*-glycero-phosphoglycerol
PAMPs	Pathogen-associated molecular patterns
PRRs	Pattern recognition receptors
HNF	Hepatocyte nuclear factor
cBB	Cured barramundi brain
PEDV	Porcine epidemic diarrhea virus
PRV	Pseudorabies virus
TGEV	Transmissible gastroenteritis virus
PRRSV	Porcine reproductive and respiratory syndrome virus
RV	Rotavirus
QCM-D	Quartz crystal microbalance with dissipation monitoring

Introduction

Antimicrobial peptides are ribosomally synthesized peptides less than 10 KDa molecular weight and having a positive net charge. These are evolutionarily preserved components (Arockiaraj et al. 2012; Shabir et al. 2018) which have a key role in the first line of defense mechanism (Hancock 2000; Arockiaraj et al. 2013) and play a major role

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in innate immunity (Campagna et al. 2007; Moon et al. 2007; Kumaresan et al. 2015). AMPs are derived from protein sequence by hydrolytic degradation which includes a signal sequence. AMPs are classified into five, based on their secondary structure which includes α-helical (Zasloff 2002; Arockiaraj et al. 2014a), β-sheet, (Andreu and Rivas 1998; Chaurasia et al. 2014) loop, extended coil and cyclic peptides (Hu et al. 2006; Arasu et al. 2017a; Shabir et al. 2018). AMPs have been derived from various vertebrates and invertebrates and even from plants (Lee et al. 2007; Katzenback 2015; Arockiaraj et al. 2015). They are very sensitive against different pathogenic microbes such as bacteria, fungi, viruses and parasites (Jenssen et al. 2006; Sung et al. 2008; Niu et al. 2013; Arasu et al. 2017b). It has a potential value as it is active against multi-drug resistant and biofilm-forming microorganisms (Hiemstra et al. 2016; Ravichandran et al. 2016), thus can replace antibiotics (Lee et al. 2007; Arockiaraj et al. 2014b).

The AMPs are short sequences present in mucosal, skin surfaces and mast cells of different aquatic organisms (Silphaduang et al. 2006; Arasu et al. 2014). As the surrounding environment of fish contains a wide range of pathogenic organisms, the innate immune system of fish has its importance (Bulet et al. 2004; Sathyamoorthi et al. 2017). The major route for entry of pathogenic microorganisms is through the epithelial cells of skin, gills and gastrointestinal tract, which provide the first line of defense by producing host defense peptides. The healthy fish can limit these infections by the presence of AMPs as well as other short defense proteins (Salger et al. 2016; Ravichandran et al. 2018). The AMPs present in the fish mucus prevents the colonization of bacteria, fungi, parasites and other pathogenic organisms (Pálffy et al. 2009; Shabir et al. 2018; Sannasimuthu et al. 2018). The presence of MHC I loci and the unique organization of the Toll-like receptor (TLR) in Atlantic cod (*Gadus morhua* L.) helps the innate immune mechanism, thus preventing pathogenic infection (Star et al. 2011; Ravichandran et al. 2017). The peptides with antimicrobial properties play a major role in such a preventive mechanism (Ruangsri et al. 2012a; Marimuthu et al. 2015). Along with antimicrobial property, these peptides also have anti-inflammation, wound healing, immune activation (Gordon et al. 2005; Sannasimuthu et al. 2019), antitumor, immune-modulatory and antidiabetic effects (Diamond et al. 2009; Conlon et al. 2014; Timalata et al. 2015), hence these fish-derived peptides can be used as a potent product for improving immunity as well as health-related matters for various organisms including human (Salger et al. 2016; Kumaresan et al. 2019). In 1990s, identification and analysis of fish AMPs were initiated; and based on their structure, they were classified into five different families such as hepcidins, β-defensins, histone-derived peptides, cathelicidins and fish-specific piscidins (Katzenback 2015; Rajesh et al. 2018).

Apart from hepcidin present in human, it was also screened in fish species. It is a major component of innate immunity with antimicrobial activity. The gene expression showed that it is highly expressed in liver tissues (Wang et al. 2009; Sathyamoorthi et al. 2019). It has a small cysteine rich region with antimicrobial property and also has a role in iron homeostasis (Rodrigues et al. 2006; Akila et al. 2018). Hepcidin were formerly called as LEAP (Liver Expressed Antimicrobial Peptide) that contains a disulphide (cysteine) bond with β sheets (Cuesta et al. 2008; Sannasimuthu and Arockiaraj 2019). The importance of hepcidin in pharmaceuticals are for its anticancer and antibacterial properties (Chen et al. 2009a, b; Thirumalai et al. 2014). Wang et al. (2010) reported that hepcidin can be used as antiviral agent against nervous necrosis virus.

Defensins are components involved in innate molecules which include antimicrobial peptides and proteins (AMPPs). It is a cationic peptide with β-sheet structure which has biological properties and are conserved among plant and animal kingdoms. Fish defensins were first found in zebrafish (*Danio rerio*), green-spotted pufferfish (*Tetraodon nigroviridis*) and tiger pufferfish (*Takifugu rubripes)* through gene mining and later it was found in other fish species too (Ruangsri et al. 2013; Purabi et al. 2020). B-defensins were reported to be present in brain, pituitary and testis and possessed antibacterial and antiviral properties (Jin et al. 2010; Raju et al. 2020). Studies on antiparasitic property were also analyzed against *Trypanosoma cruzi* and *Toxoplasma gondii* by pore formation and mitochondrial DNA fragmentation (Masso-Silva and Diamond 2014). The antiviral activity of defensin was isolated from *Epinephelus coioides* and was used against two viral pathogens, Singapore grouper iridovirus (SGIV), an enveloped DNA virus and viral nervous necrosis virus (VNNV), a non-enveloped RNA virus (Guo et al. 2012).

The histone derived peptides are a part of histone molecule with biological activities. Buforin I was isolated from Asian toad (*Bufo bufo*) and was the first histone H2A derived peptide. These histone derived peptide was found in many fish species with wide range of pathogenic activities (Masso-Silva and Diamond 2014; Prabha et al. 2019). The histone-derived AMPs were identified from fish species including catfish (*Parasilurus asotus*), Atlantic salmon (*Salmon salar*), rainbow trout (*Oncorhynchus mykiss*), and Atlantic halibut (*Hippoglossus hippoglossus*) and invertebrates pacific white shrimp (*Litopenaeus vannamei*) and Chinese scallop (*Chlamys farreri*) (Zoysa et al. 2009). The two major histones are core histones and linker histones such as H2A, H2B, H3, H4 and H1. Parasin, hipposin, buforin I and II, abhisin, himanturin, sunettin, and molluskin are represent histone H2A-derived peptides; and onchorhyncin II and SAM (Salmon antimicrobial protein) are represent histone H1 (Chaithanya et al. 2013).

Cathelicidin peptide has four cysteine residues forming two disulphide bridges, which is cationic and amphipathic in nature. Maier et al. (2008) suggested that it has major role in both innate and adaptive immunity. In mammals, both immune and non-immune activities have been exhibited. The gene expression was induced by different bacterial species and the expression were high in gill, liver, spleen and intestine (Masso-Silva and Diamond 2014). The major property of this peptide is its antimicrobial activity with no cytotoxicity (Lu et al. 2011).

Piscidin are a linear cationic α-helical peptide with broad-spectrum activity (Fernandes et al. 2010). These peptides were characterized in various species of teleost fish which comes under superorder Acanthopterygii (Ruangsri et al. 2012b; Elumalai et al. 2019). Piscidin contains amino acid sequences in length between 18 and 46. The first cationic AMP of piscidin was isolated from hybrid striped bass (*Morone saxatilis* × *M. chrysops*) (Chinchar et al. 2004; Campagna et al. 2007; Lauth et al. 2001). It exhibits antibacterial, antifungal and antiviral properties. This peptide is also showed an innate immune response against parasitic infections (Dezfuli et al. 2010; Niu et al. 2013). It was reported that piscidin was sensitive towards fish and human pathogens and multidrug-resistant bacteria such as MRSA ¼ methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococci* sp., etc., (Lauth et al. 2001; Noga et al. 2009; Dezfuli et al. 2010). This review is especially dealing with the structure, types, mode of action, properties including cytotoxicity and membrane permeabilization and therapeutical properties of fish-derived piscidin.

Distribution of Piscidin

Piscidins are present in different taxa of teleosts including the families of Moronidae, Siganidae, Sciaenidae, Percichthyidae, Belontidae, Latridae (Andrews et al. 2010), Cichlidae, Sygnathidae (Sun et al. 2012) and Sparidae (Corrales et al. 2009). There is an evidence that piscidin is also present in families including Gasterosteidae, Sebastidae, Adrianichthyidae, Fundulidae, Cyprinodontidae and Anoplopomatidae, which was confirmed by Expressed Sequence Tag (EST) databases (Salger et al. 2017).

The piscidin gene transcript was present in striped bass (*M. saxatilis*), white bass (*M. chrysops*), mandarin fish (*Siniperca chuatsi*), European seabass (*Dicentrarchus labrax*), Nile tilapia (*Oreochromis niloticus*), *Gadus morhua* (Salger et al. 2016), hybrid striped bass (Salger et al. 2011) and *Dicentrarchus labrax* belongs to Moronidae (Salerno et al. 2007). The presence of piscidin gene transcript was also observed in *Siganus rivulatus*, *Leiostomus xanthurus* and *Micropogonias undulates* belongs to Siganidae family. There is an evidence for the presence of the same in *Siniperca chuatsi* and *O. niloticus* belongs to Percichthyidae and Cichlidae family, respectively (Acosta et al. 2013; Sun et al. 2007; Peng et al. 2012b). *Trichogoster leeri*, a Belontidae family also has a piscidin amino acid sequence in common. *Epinephelus niveatus*, which belongs to Serranidae family has the piscidin sequence in it (Silphaduang et al. 2006). The sequence of chrysopsins isolated from *Chrysophrys major*, a member of Sparidae family, which is similar to piscidin (Iijima et al. 2003). The expressed sequence tag (EST) databases showed evidence that piscidin was also isolated from *Gasterosteus aculeatus*, belongs to Gasterosteidae family (Brown et al. 2008). It is reported that piscidin was isolated from Sebastidae family which includes *Sebastes caurinus* and *S. schlegelii* (Heras et al. 2011). Moreover, presence of piscidin was reported in *Oryzias latipes*, belongs to Adrianichthyidae and *Fundulus heteroclitus*, belongs to Fundulidae family. *Cyprinodon variegatus* contains a piscidin sequence that was belong to Cyprinodontidae family; a similar piscidin sequence was reported in *Anoplopoma fimbria* from Anoplopomatidae family (Iijima et al. 2003; Brown et al. 2008). The piscidin like peptide was also isolated from orange-spotted grouper (*Epinephelus coioides*), red-spotted grouper (*E. akaara*), brown-marbled grouper (*E. fuscoguttatus*), sablefish (*Anoplopoma fimbria*), spotted seahorse (*Hippocampus kuda*), yellow croaker (*Larimichthys crocea*) (Ruangsri et al. 2012b) and *Gadus morhua* (Noga et al. 2009). Until now, it is reported that piscidin is only peptide present in superorder Acanthopterygii.

Other AMPs of Piscidin Family

Considering the piscidin family, it consists of many other peptides under its family including pleurocidin, moronecidin, dicentracin, epinecidin, chrysophsin, myxindin, misgurin and gaduscidin (Salerno et al. 2007; Sun et al. 2007; Peng et al. 2012b; Acosta et al. 2013; Katzenback 2015). Table 1 shows the amino acid sequence, charge, expression pattern, presence and properties of different AMPs of piscidin family.

Pleurocidin is a highly basic molecule and an amphipathic α-helical cationic peptide found in skin, gill and gut tissues of winter flounder (*Pseudopleuronectes americanus*) (Browne et al. 2011) and its antimicrobial activities was examined (Patrzykat et al. 2002). Piscidin has a similarity with pleurocidin as well as a close genetic relationship which suggests that pleurocidin are the members of piscidin family. Pleurocidin and pleurocidin like peptides were also isolated from Atlantic halibut (*Hippoglossus hippoglossus*), witch flounder (*Glyptocephalus cynoglossus*), American plaice (*Hippoglossoïdes platessoïdes*) and yellowtail flounder (*Limanda ferruginea*) (Heras et al. 2011; Ruangsri et al. 2012b). It has a broad spectrum of activity against

Table 1 List of different antimicrobial peptides belong to piscidin family

AMPs	Sequence	Charge	No. of residues	Expression site	Sources	Properties	References
Pleurocidin	GWGSFFKKAAHVGKHVG-KAALTHYL	4	25	Gills, skin, spleen, kidney and intestine	*Pleuronectes americanus*	Antibacterial, antifungal, antiviral, antiparasitic, immunomodulation and chemotaxis	Shabir et al. (2018)
Moronecidin	FFHHIFRGIVHVGKTIH(K/R) LVTGT	3	22	Skin, gills, blood, intestine, kidney and spleen	*Morone* sp.	Antibacterial, antifungal and causes necrosis.	Lauth et al. (2001) and Shabir et al. 2018)
Epinecidin-1	GFIFHIIKGLFHAGKMIHGLV	3	21	Gills and intestine	*Epinephelus coiodes*	Anti-bacterial, antifungal, Anti-cancer, antiviral and Wound healing	Lin et al. (2009a, b) and Shabir et al. (2018)
Misgurin	RQRVEELSKFSKKGAAARR RK	7	21	Skin	*Misgurnus* sp.	Anti-bacterial and antifungal	Yan and Wu (2012) and Shabir et al. (2018)
Chrysophin	FFGWLIKGAIHAGKAIHGL-HRRRH	5	22	Gills and skin	*Chrysophrys major*	Antimicrobial	Salerno et al. (2007)
Myxinidin	GIHDILKYGKPS	2	12	Epidermal mucus	*Myxine glutinosa*	Antibacterial and antibiofilm	Han et al. (2016)
Dicentracin	FFHHIFRGIVHVGKSI-HKLVTG	3	22	Granulocytes, macrophages and monocytes	*Dicentrarchus labrax*	Antimicrobial	Salerno et al. (2007)
Gaduscidin	FIHHIIGWISHGVRAIHRAIH	3	21	Spleen, head, kidney and gill	*Gadus morhua*	Antimicrobial and antibiofilm	Browne et al. (2011)

The table describes the peptide sequence and other parameters including the charge, number of residues, expression site, source of presence and their properties

Gram-positive and Gram-negative bacteria. The sequence has been arranged as $^{H-}$Gly-Trp-Gly-Ser-Phe-Phe-Lys-Lys-Ala-Ala-His-Val-Gly-Lys-His-Val-Gly-Lys-Ala-Ala-Leu-Thr-His-Tyr-Leu^{-OH} (Yoshida et al. 2001). Pleurocidin has homology with dermaseptins (from skin of hylid frog) and ceratatoxins (from mediterrenean fruit fly) and is showing high antifungal activity (Jung et al. 2007). It is capable of causing dye leakage from liposomes, translocate across model membranes and pore-forming activity in planar lipid bilayers (Mason et al. 2006). The mode of action against the microbes was developed by membrane disruption mechanism by binding pleurocidin on microbial membrane (Jung et al. 2007). It is reported to show membrane disruption and oxidative stress with no hemolysis against human erythrocytes. The therapeutic application of pleurocidin against infectious diseases was reported by Choi and Lee (2012) with combination of other drugs and along with adjuvants. The pleurocidin were used for cancer treatment in zebrafish model (Morash et al. 2011). Thus, it was suggested to use in aquaculture as therapeutic agent and it is also used as a potential food preservative (Burrowes et al. 2006).

Moronecidin was isolated from gill, skin, intestine, spleen, head kidney and blood of hybrid striped bass and white bass (*M. chrysops*) (Browne et al. 2011); it is function against various bacterial pathogen. It is a novel helical AMP with 22 amino acid residue, which is C-terminally amidated (Lauth et al. 2001). This peptide have low toxicity and high salt tolerance (Shin et al. 2017). The moronecidin mRNA was upregulated in skin, heart, brain, gill, head kidney, kidney, intestine and spleen due to the induction of *Escherichia coli* LPS as well as *Streptococcus iniae* (Browne et al. 2011). The membrane disruption of moronecidin on microbes is due to the formation of pores. As it has salt tolerance, it can be used for therapeutic applications in marine organisms as well as human medicines (Lauth et al. 2001). The toxicity of moronecidin were analysed in murine and human hepatic cells, which resulted no cytotoxicity, thus it can be used as a therapeutic agent at safe concentration (Bo et al. 2019).

Dicentracin belongs to the piscidin family derived from European seabass (*Dicentrarchus labrax*) (Family: Moronidae) (Andrews et al. 2010; Rondeau et al. 2013). The novel amphipathic alpha helical peptide isolated from sea bass contains 22 amino acid residues and is having antibacterial, antiviral and antiparasitic activities (Meloni et al. 2015). It was also reported that dicentracin possessed antimicrobial activity in mandarin fish against microbial pathogen (Sun et al. 2007). Its expression was observed in macrophages, granulocytes and monocytes from head kidney, peripheral blood and peritoneal cavity (Salerno et al. 2007). As reported by Terova et al. (2009) Bio-Mos induced changes in the gene expression of dicentracin in seabass.

Epinecidin, cationic peptide with α-helical structure isolated from grouper (*E. coioides*) which contains 67 amino acid residues; it shows growth inhibitory activities against a range of Gram-positive and Gram-negative bacteria and fungus (Pan et al. 2009). It interacts with phospholipids in bacterial membranes through membrane disrupting mechanism (Chen et al. 2009a, b). It is responsible for pore formation in membranes of bacteria leading to lysis and their subsequent death (Pan et al. 2007). It has an anionic prodomain COOH terminal with RRRH amino acid residue that forms a non-helical hydrophilic domain (Yin et al. 2006). It has multifunctional properties including antisepsis, antitumor, antivirus and immunomodulatory activities (Narayana et al. 2015). The mature peptide showed sequence similarities with chrysophsin, moronecidin, pleurocidin and piscidin 3 (Pan et al. 2007). The major advantage is that it has the ability to target cancer cells with minimum cytotoxicity (Lin et al. 2009a, b). It can also be used as cleaning agent to prevent pathogenic infections (Pan et al. 2010) due to tis antimicrobial properties (Chee et al. 2019).

Chrysophsin was isolated from red sea bream (*Pagrus major*) which is similar to piscidin, pleurocidins and epinecidin that present in various fishes (Brown et al. 2008; Salger et al. 2016). Chrysophsin-1, chrysophsin-2 and chrysophsin-3 are present in the eosinophilic granule cells in gills; and has potent bactericidal activity against Gram-negative and Gram-positive pathogens of fish as well as crustaceans. The C-terminal region forms RRRH with a non-helical hydrophilic domain similar to epinecidin (Iijima et al. 2003). Costa et al. (2018) staed that chrysophin-1 peptide were covalently immobilized which result in higher antimicrobial activity than when the peptide is simply adsorbed. The disruption process of Chrysophin-3 were analyzed using Quartz Crystal Microbalance with Dissipation monitoring (QCM-D) by membrane permeabilization through pore formation (Michel et al. 2017).

Myxindin was isolated from the mucus layer of *Myxine* sp. (Ebbensgaard et al. 2015). It has activity against both Gram-positive and Gram-negative bacteria and even multidrug-resistant strains. It has the ability to disrupt bacterial membrane by pore formation and can be used for therapeutic agent development. It is not toxic even at high concentrations, thus has no significant hemolysis activity (Han et al. 2016). Some of the report contradict the activities of chrysophin peptide too (Ebbensgaard et al. 2015).

Misgurin, a 21 amino acid peptide found in loach (*Misgurnus anguillicaudatus*) with a broad spectrum of antimicrobial activity and has no significant hemolytic properties. It has activity against Gram positive bacteria, Gram negative bacteria and fungi species (Shabir et al. 2018). The sequence did not show any homology with other known AMPs. It acts as non-specific defense substance in fish skin. This peptide have a strong cationic tetrapeptide sequence 'RRRK' at the C-terminal region 'Arg-Gln-Arg-Val-Glu-Glu-Leu-Ser-Lys-Phe-Ser-Lys-Lys-Gly-Ala–Ala-Ala-Arg-Arg-Arg-Lys' (Park et al. 1997; Iijima et al. 2003).

Gaduscidin has two isomers namely Gad-1 and Gad-2 which was identified from the expressed sequence tag database of an *G. morhua*; both isomers have potential antimicrobial properties (McDonald et al. 2015). Its expression was observed in head, spleen, kidney, gill, peripheral blood, pyloric caecum and brain. The high level of gene expression of gaduscidin are consistent with the immune functions of these tissues in teleosts. However, it was hardly induced in spleen due to intraperitoneal injection of bacterial antigens (Brown et al. 2008). The crude protein extracts of gaduscidin also contains high antimicrobial activities. This peptides has several histidine residues, for example, Gad-1 has five and Gad-2 has four (McDonald et al. 2015).

Isoforms and Classes of Piscidin

Piscidin was present as different isomers in various fish species. Though they are structurally similar, they are functionally different. Piscidin 1 was first isolated from mast cells of the hybrid striped bass (Lee et al. 2014); it contains a potent AMP of 22 amino acid sequence which is conserved with other isoforms of piscidin in the amino terminus, where histidine and phenylalanine are rich. It is active against fungi, yeast, viruses, parasites, Gram-positive and Gram-negative bacteria and even active against antibiotic-resistant bacteria. As it has some hemolytic and cytotoxic effects, its therapeutic usage has been limited (Lee et al. 2007). It has the highest antibacterial activity among other piscidins (Lauth et al. 2001; Noga and Silphaduang 2003). Piscidin 1 was reported to have potent antimicrobial activity against Methicillin Resistant *S. aureus* (Menousek et al. 2012). It has the ability to permeabilize cancer cell membranes by interacting with a negative charge on their membranes. As lipids get through the alpha-helix of piscidin, it forms a toroidal hole lined by peptides and lipid groups (Lin et al. 2012).

Piscidin 2, a 22 amino acid residue with a conserved amino-terminal, rich in histidine and phenylalanine (Sung et al. 2008). Piscidin 2 differs to piscidin 1 only by single amino acid substitution at its 18th position and has an identical antimicrobial property (Colorni et al. 2008). It showed activity against viruses, fungi and bacteria, even against antibiotic-resistant bacteria (Lauth et al. 2001; Sung et al. 2008). Piscidin 2 is active against infective stages of parasites and is a potent component of antimicrobial defense in various fish species (Lee et al. 2014). Piscidin 2 is a lytic peptide which disrupts the permeability of microbial membrane leading to lysis of the cell. The parasite, *Ichthyophthirius multifiliis* was sensitive towards the exposure of piscidin 2 showing a lethal effect. Due to low cation concentration in freshwater, the sensitivity is more. As seawater has high concentrations of monovalent and divalent cations, they are inhibitory to most of the antibiotics. Comparatively, the peptide is active in salt and it is active against marine parasites as well. It was also reported that piscidin 1 and 2 are highly active against *S. aureus* even in the presence of high concentration of monovalent and divalent cations (Colorni et al. 2008). Piscidin 1 and 2 were also derived from skin and gill tissues of striped bass (Campagna et al. 2007).

Piscidin 3 is 22 amino acid in length; also, it is a cationic, amphipathic and membrane disruptive peptide with high histidine residues. It has shown anti-inflammatory properties both in in vitro and in vivo condition and can also be used as an anesthetic compound (Hayden et al. 2015). Piscidin 3 has an antiparasitic activity in which the mechanism is undetermined, and it is inhibitory to all bacterial pathogens as like piscidin 1 and 2 (Colorni et al. 2008). Compared to piscidin 2 and piscidin 1, piscidin 3 showed low minimum inhibitory concentration and minimum bacterial concentration (Moon et al. 2007). It is also showed low amphipathicity as it has a glycine at its 17th position (Lee et al. 2007). The piscidin 1, 2 and 3 are highly basic with isoelectric points ranged between 11.27 and 12.3.

Piscidin 4 is a 44 amino acid length peptide (Salger et al. 2011) with a molecular weight of 5329 Da and its N-terminus was highly homologous to other piscidins like Pis-1, Pis-2 and Pis-3. Piscidin 4 has pI of 11.23, which is highly basic in nature and they form a large hydrophobic region due to the presence of Phe^{2}, Leu^{5}, Phe^{6}, Ala^{9}, Ile^{12}, Phe^{13}, Ala^{16}, Trp^{20} and Val^{34} in the sequence; altogether these residues formed a helix and loop regions (Noga et al. 2009). It has antibacterial activity against both Gram-negative and Gram-positive bacteria including pathogens causing pasteurellosis and lactococciosis (Salger et al. 2011; Peng et al. 2012b) caused by *Photobacterium damselae* subsp., piscicida and *S. iniae*. They are also active against multi-antibiotic resistant strains of *L. garviae* and even against some human pathogens. Piscidin 4 has a coil at the C-terminal end which separates two β-sheet (Lauth et al. 2001) and alpha-helix at the N-terminal, and it was present both in white bass and striped bass. This peptide has a modified amino acid on its 20th position which is a hydroxylated tryptophan based on mass spectrometry analysis and the Schiffer-Edmunson plot; both the reports suggest that piscidin 4 has an amphipathic α-helix structure (Park et al. 2011). As piscidin 4 has more glycine and proline residues than piscidin 1, it shows more α-helicity that causes flexibility and bending (Lee et al. 2007).

Piscidin 5 was reported from *M. chrysops* and it was highly expressed in the intestine. The β-sheets present in piscidin 4 and 5 are similar to carbohydrate and lipopolysaccharide-binding motifs which helps in pattern recognition function in innate immunity (Yoshida et al. 2001; Lauth et al. 2001; Patrzykat et al. 2002; Mason et al. 2006). Piscidin 5 is a mature peptide with 44 amino acids that contains a signal peptide with 22 amino acid at N terminal and 4 amino acid as prodomain at C-terminal (Pan et al. 2018). Piscidin 5 like peptide plays an immune response in large yellow croaker (*Larimichthys crocea*). It was showing 86% similarity with other homologous species (Zhou et al. 2014).

Piscidin 6 and 7 belongs to Class III family based on their structure as well as function. Piscidin 6 gene expression was predominantly observed in gill, intestine and kidney of *M. saxatilis* and *M. chrysops*. Also, piscidin 7 was expressed in the intestine of *M. saxatilis* (Campoverde et al. 2017). The different isomers of piscidin, their amino acid sequence and physico-chemical properties including isolelctric point and molecular weight are listed in Table 2.

Piscidin family were classified into three major classes based on the number of amino acid residues present in it. Piscidin 1, 2 and 3 belong to Class I while piscidin 4 and 5 belong to Class II and piscidin 6 and 7 belong to Class III family. Class I has 22 amino acid residues, whereas Class II and Class III has 44–46 and 55 amino acid residues, respectively (Salger et al. 2016). Class I piscidins have the highest activity against Gram-positive bacteria compared to Class II and class III piscidins. Class I piscidin showed higher activity against prokaryotes and ciliated protozoans compared to class II and class III (Campoverde et al. 2017). Class II piscidins have the highest activity against Gram-negative bacteria and Class III piscidins have very little activity against bacteria, whereas high activity was reported against protozoan (Salger et al. 2016; Shin et al. 2017). Class III piscidins has coil-β sheet-coil-α helix structure which is different from that of Class I and Class II (Salger et al. 2016). The seven piscidins isolated from different fish sources and the classification was listed in Table 3.

Structure of Piscidin

The structure of piscidin was determined by Nuclear Magnetic Resonance (NMR) spectroscopy; it shows that piscidin 1 formed an α-helical structure in SDS micelles (Jeong

Table 2 List of different isomers of piscidins, their sequence and other parameters including number of residues, isoelectric point, molecular weight and their properties

Peptide	Sequence	No. of residues	Isoelectric point	Mol. mass (Da)	Properties	References
Piscidin 1	FFHHIFRGIVHVGK-TIHRLVTG	22	12.01	2572.06	Anti-viral, anti-bacterial, anti-fungal, anti-parasitic and anticancer	Salerno et al. (2007) and Chen and Cotten (2014)
Piscidin 2	FFHHIFRGIVHVGKTI-HKLVTG-NH2	22	11.27	2543.4	Anti-viral, anti-bacterial, anti-fungal, anti-mold and anti-parasitic	Chen et al. (2009a, b), Sung et al. (2008), Salger et al. (2011) and Peng et al. (2012a)
Piscidin 3	FIHHIFRGIVHAGRSI-GRFLTG	22	12.3	2491.93	Anti-viral, anti-bacterial, anti- fungal and anti-parasitic	Chen et al. (2009a, b) and Salger et al. (2011, 2016)
Piscidin 4	FFRHLFRGAKAIFR-GARQGXRAHKVVS-RYRNRDVPETDN-NQEEP	44–46	11.23	5329.3	Lowest hemolysis	Yoshida et al. (2001) and Peng et al. (2012a)
Piscidin 5	LIGSLFRGAKAIFR-GARQGWRSHKA	44–46	12.48	2784.27	Anti-bacterial, anti-fungal and anti-parasitic	Sun et al. (2007) and Rathinakumar et al. (2009)
Piscidin 6	N/A	55	N/A	6229	Antibacterial	Salger et al. (2016)
Piscidin 7	N/A	55	N/A	6318	Antibacterial	Salger et al. (2016)

Table 3 Isomers of piscidin peptides and their different classes obtained from different species have been provided along with its GenBank accession IDs

Peptide	GenBank accession ID (species)	Class	Organism	References
Piscidin 1	AF394243 (white bass), JX412481 (Malabar grouper)	Class I	*Morone chrysops*, *Epinephelus malabaricus*	Sun et al. (2007)
Piscidin 2	JX412480 (Malabar grouper), AF394244 (striped sea-bass)	Class I	*Epinephelus malabaricus*, *Morone saxatilis*	Sun et al. (2007)
Piscidin 3	KX231319 (striped bass), KX231323 (white bass)	Class I	*Morone chrysops*, *Morone saxatilis*	Salger et al. (2016)
Piscidin 4	KX231324 (white bass), KX231315 (striped bass), HM596029 (white bass × striped sea-bass)	Class II	*Morone chrysops*, *Morone saxatilis* *Morone chrysops* × *Morone saxatilis*	Sun et al. (2007) and Salger et al. (2016)
Piscidin 5	KX231312 (white bass), KX232424 (striped bass), HM596030 (white bass × striped sea-bass)	Class II	*Morone chrysops*, *Morone saxatilis*, *Morone chrysops* X *Morone saxatilis*	Sun et al. (2007) and Salger et al. (2016)
Piscidin 6	KX232425 (white bass X striped sea-bass), KX231321 (striped sea-bass), KX231326 (white bass)	Class III	*Morone chrysops* × *Morone saxatilis*, *Morone saxatilis*, *Morone chrysops*	Salger et al. (2016)
Piscidin 7	KX231322 (striped sea-bass), KX231318 (white bass X striped sea-bass)	Class III	*Morone saxatilis*, *Morone chrysops* × *Morone saxatilis*	Salger et al. (2016)

et al. 2016). Utilizing dodecyl phosphocholine (DPC) micelles, a zwitterionic lipid surface the three-dimensional structure was determined (Campagna et al. 2007). Piscidin-1 has an amphipathic α-helical structure, as it contains hydrophobic and hydrophilic amino acids in opposite sides which was determined by solid-state NMR (Lee et al. 2007). The solid-state NMR study shows that Pis-1 is parallelly oriented to membrane surface. The peptide-lipid interactions are enhanced by water-bilayer interface of amphipathic cationic AMPs (Lee et al. 2007). As reported Perrin et al. (2014) utilizing 3:1 ratio of 1,2-dimyristoyl-sn-glycero-3-phosphatidylcholine (DMPC)/1,2-dimyristoyl-sn-glycero-3-phosphatidylglycerol (DMPG) and 1-palmitoyl-2-oleoyl-sn-glycerophosphatidylethanolamine (POPE)/1-palmitoyl-2-oleoyl-sn-glycero-phosphoglycerol (POPG) lipid bilayers, different high-resolution structures

of piscidin 1 and piscidin 3 were determined (Perrin et al. 2014). In a circular dichroism analysis, Piscidin 2 was unstructured in the water while in trifluoroethanol showed α helical structure (Lauth et al. 2001; Sung et al. 2008). The prediction of the secondary structure of piscidin 4 suggested an alpha-helix in N-terminal and a random coil in the C-terminal of the sequence (Noga et al. 2009). Piscidin 4 has high activity towards DPPC and EYPC liposome which contain low alpha-helical regions (Lee et al. 2007). The piscidin 5 like peptide is more similar to piscidin 4; and piscidin 5 has a major role in immune response (Zhou et al. 2014).

The structural diversity of piscidin is due to the adaptation of microbes in different environments (De Angelis et al. 2011). Kumaresan et al. (2018) have identified two isoforms of piscidin, which has conserved as well as variable regions with three distinct α-helices. The three-dimensional structure of piscidin was depicted in Fig. 1 (Kumaresan et al. 2019).

Gene Regulation of Piscidin

Piscidin was found as conserved among teleosts and it was upregulated by various pathogenic responses. This regulation towards pathogenic challenge is species and gene-specific; the regulation of piscidin was recognized by pathogen-associated molecular patterns (PAMPs) via pattern recognition receptors (PRRs), such as the action of an intracellular signaling cascade which includes MyD88,

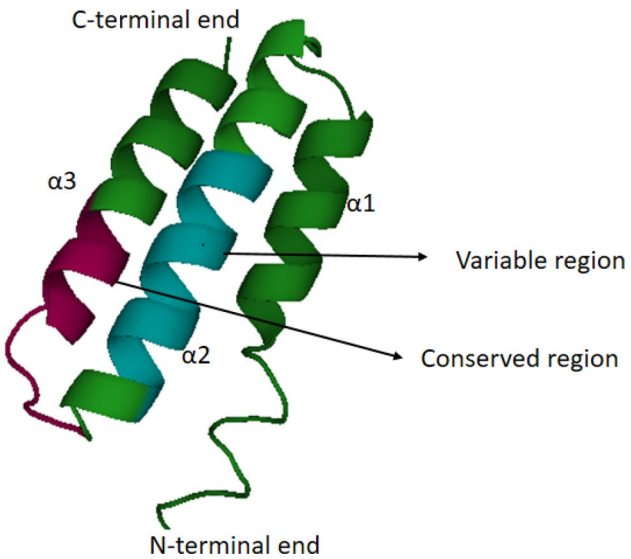

Fig. 1 Three-dimensional structure of piscidin protein. Piscidin protein was isolated from *Channa striatus* (LS974203) with conserved and variable regions highlighted in magenta and blue color, respectively. This structure was formulated using I-Tasser server (Color figure online)

Toll-like receptors (TLRs), TRAF6, IRAK1 and IKK. The signaling cascade helps in the activation of NF-κB which translocates to the nucleus, where AMPs and effector molecules transcriptionally activated (Campoverde et al. 2017). Piscidin expression was observed in Nile tilapia, rodlet cells of mesentery organs, phagocytic granular cells of head kidney and gills of gilthead seabream (*Sparus aurata*) (Mulero et al. 2008) and in alimentary tract and gill of pearl gourami (*Trichogaster leeri*) (Silphaduang et al. 2006; Ruangsri et al. 2012b). The up and down-regulation of the different classes of piscidins against various pathogens in fish species are presented in Table 4. In fish, piscidins are received by a pathogen that contains phagosomes, thus the peptides act as an antimicrobial agent for bactericidal activity through phagocytosis due to the granules present in the phagocytic granulocytes of piscidin (Iijima et al. 2003; Andrews et al. 2010). The positively charged sites present in the piscidin gene codes for mature peptide which provide protection against evolving host pathogens (Peng et al. 2012a). Piscidin was introduced by some stimuli like Gram-positive and Gram-negative bacteria, bacterial cell components like LPS, bacterial antigen like ASAL and also by parasites, viruses and poly I:C (Masso-Silva and Diamond 2014).

Most piscidin genomic organization have four-exon and three-intron (Cole et al. 2000), whereas piscidin from Nile tilapia has a three-exon and two-intron in structure (Peng et al. 2012a). The epinecidin from yellow croaker and grouper has five-exon and four-introns (Pan et al. 2008). The proteolytic cleavage at N-terminal and prepropeptide of C-terminal leads to the removal of the signal peptide and prodomain, respectively; hence, releasing a short-matured peptide, piscidin. Piscidin has an amphipathic structure with hydrophilic cationic amino acids and can, therefore, interact with pathogenic membranes (Bae et al. 2014). During fish development, the piscidin expression was upregulated. The levels of gene expression of piscidin are noticed in skin mucus, skin, gill, head kidney, intestine/gastrointestinal tract, spleen, blood, liver, rectum, gall bladder, stomach, pyloric caeca, heart and muscle as high to low (Iijima et al. 2003; Salger et al. 2011). Most commonly piscidins are present in mast cells of gills and rodlet cells of skin, intestine, gill, epithelial mucous cells, eosinophilic granular cells, phagocytic granulocytes and intestinal goblet cells of intestinal mucosa (Katzenback 2015). The promoter regions of piscidin contains binding sites namely γ-IRE, α-IRE, C/EBPβ, NF-IL-6, AP-1 and hepatocyte nuclear factor (HNF-1) transcriptional factors; these receptors involved in intracellular signaling pathway and transcriptional factors in piscidin regulation (Lee et al. 2014; McDonald et al. 2015; Pan et al. 2007; Han et al. 2016; Campoverde et al. 2017).

Piscidin has an immune-modulatory role that expresses both pro-inflammatory genes and immune-related genes such as IL-10, IL-1β, TNF-α, NOS2, NF-kb, Myd88, TLR3,

Table 4 List of pathogens influenced the up and downregulation of piscidin protein along with their expression sites and organisms

Pathogens	Expression site/ tissues	Upregulation/ downregulation	Organism	References
Gram-negative bacteria				
Aeromonas salmonicida	Head kidney and spleen	Upregulation	*Gadus morhua*	Brown et al. (2008)
Edwardsiella tarda	Spleen and kidney	Up and downregulation	*Oplegnathus fasciatus*	Narayana et al. (2015)
LPS	Brain, heart, gill, kidney, pronephros, skin, spleen, intestine, head kidney leukocytes, head kidney, intestine and skin	Upregulation	*Siniperca chuatsi*, *Chionodraco hamatus* and *Epinephelus coioides*	Ii (2010), Pan et al. (2007) and Yang et al. (2016)
Vibrio anguillarum	Skin, gills, head and kidney	Up and downregulation	*Dicentrarchus labrax*	Salger et al. (2016)
Gram-positive bacteria				
Streptococcus iniae	Kidney, spleen and gill	Upregulation	*Oplegnathus fasciatus*	Narayana et al. (2015)
Virus and viral analogue				
Lymphocystis iridovirus	Acidophilic granulocytes	Upregulation	*Sparus aurata*	Iijima et al. (2003)
Poly I:C	Head kidney, leukocytes, intestine and skin	Upregulation	*Chionodraco hamatus* and *Epinephelus coioides*	Ii (2010) and Pan et al. (2007)
Red seabream iridovirus (RSIV)	Spleen and kidney	Upregulation	*Oplegnathus fasciatus*	Narayana et al. (2015)
Parasites				
Acanthocephalus lucii	Intestine mast cells	Upregulation	*Perca fluviatilis*	Han et al. (2016)
Chondracanthus goldsmidi	Gills	Upregulation	*Latris lineata*	Sun et al. (2012)
Cryptocaryon irritans	Gills, skin, spleen, head kidney, liver and intestine	Upregulation	*Pseudosciaena crocea*	Niu et al. (2013)
Ergasilus sp.	Gill mast cells	Upregulation	*Sparus aurata*	McDonald et al. (2015)

TLR1 and TLR4a by releasing NF-κB via IKB down-regulation; also, there is a down-regulation of some anti-inflammatory signals. In addition, a reduction of inflammatory cytokines by pathogen expression was observed in fishes (Menousek et al. 2012; Noga et al. 2009; Sun et al. 2007). Immunomodulatory activity of pleurocidin belongs to piscidin family in which expression of IL-1β and COX1 was induced by RTS11 macrophage cell line, where no effect was observed on antigen presentation or Mx gene expressions by JAK/STAT (Chiou et al. 2006); Mx protein is the interferon-induced antiviral protein, a product of the Mx gene (Jensen and Robertsen 2000). The Mx proteins have a role in resistance to negative-stranded RNA viruses, thus function as antiviral defense (Trobridge and Leong 1995). Pleurocidin does not affect the LPS induced responses, while cured barramundi brain (cBB) fish cell line induced Mx transcripts (Wang et al. 2010). In response to piscidin transcripts, Mx2 and Mx3 were down-regulated in grouper (Wang et al. 2010). In transgenic zebrafish epinecidin-1 expression was induced due to pathogenic microbes (Peng et al. 2010). When the fish is expressing epinecidin-1 due to *E. coli*, the expression of TNF, IL-1β, TLR4, NF-κB and nitric oxide synthase 2 were also observed (Katzenback 2015). The immunomodulatory activity of piscidin in fish enabled the expression of pro-inflammatory and other immune-related genes such as IL-1β, IL-22, TNF-α, IL-26, IFN-γ, lysozyme, IL-10, NOS2, NF-κB, MyD88, TLR1, TLR4a and TLR3 (Baumann 1991; Larrick et al. 1995; Akira et al. 2006; Lee et al. 2007; Noga et al. 2009; Hayden et al. 2015).

Piscidin was expressed in fish during embryonic development and the amount of expression was increased between day 8 and day 40 (Noga et al. 2009; Shin et al. 2017). However, a reduction was observed in 40 day old larvae, it was due to the dilution effect because of the rapid growth occurred after metamorphosis. In the developed juveniles, piscidin was highly expressed in gill, moderately in kidney and spleen and lower in gut (Noga et al. 2009; Dezfuli et al. 2010).

The gene expression of piscidin 1 was only found in striped bass and piscidin 2 were only found in white bass. While Piscidin 4 gene is inherited from both or any one of the parental species of hybrid striped bass. Piscidin 4 is one of the major components of host antibacterial defenses (Noga et al. 2009). The gene expression of piscidin 4 shown in both species; mainly the highest expression was noticed in gills and the lowest was observed in the foregut of intestine (Park et al. 2011). The striped bass and white bass piscidin orthologs contributed to the alleles of the hybrid striped bass genome as six different piscidin from 4 loci (piscidin 1, 3, 4, and 6), another 2 alleles from 2 loci (piscidin 5 and 7) 1 allele from 1 loci (piscidin 2) which are all derived from parental species (Salger et al. 2016).

Mechanism of Piscidin as Antimicrobial

The AMP has a net positive charge, a high isoelectric point which interacts with negatively charged bacterial membrane, partial or complete insertion of the lipid bilayer, flexible in structure and active biological conformation on binding with membrane (De Angelis et al. 2011). The mode of action of a peptide depends on the charge, length, amphipathicity, concentration of peptide (Hayden et al. 2015) and lipid composition of the membrane (Campagna et al. 2007). The amphipathic nature of these peptides was important for their mechanism of action against bacteria as it can alter antimicrobial activity (Haney and Hancock 2013). The interfacial activity of AMPs depends on the balance of hydrophobic and electrostatic interactions of peptides with water and lipids (Ii 2010). The proteoglycan and lipopolysaccharide outer membrane of Gram-positive and Gram-negative, respectively were crossed easily by AMPs while the permeation of large marker took time (Campagna et al. 2007; Perrin et al. 2014). After the contact of AMPs with the membrane, there is a chance of disruption, destruction and fragmentation (Ii 2010).

In low peptide-lipid ratio, the peptide binds parallel to the lipid bilayer, as peptide-lipid ratio increases, the peptide starts to be perpendicular to the membrane (Park and Hahm 2005). Thus, the membrane permeabilization was explained in different models including barrel-stave, carpet-like, toroidal pore models (Campagna et al. 2007) and detergent model (Ii 2010). In the barrel-stave model, the transmembrane pore formation leads to membrane permeabilization which was made of helices (Campagna et al. 2007). In the carpet-like mechanism, the peptides act as a detergent by forming pore by disrupting the bacterial membranes (Campagna et al. 2007). The correct mode of action of peptides was not established; however, it was suggested that the bacterial cells were lysed by disruption of the bacterial cell membrane (Moon et al. 2007) and disrupt the intercellular components (Hayden et al. 2015). The piscidin peptide disrupts the bacterial cell membrane by toroidal pore mechanism; lipids of the membrane were inserted between the α-helices of peptide (Corrales et al. 2010). The piscidin AMP showed similar characteristic features based on the mechanism involved in the membrane permeabilization compared to cationic AMPs (Rahmanpour et al. 2013).

AMPs are believed to kill microorganisms in two methods of mode of action, which are non-receptor mediated process and receptor-mediated process. The Gram-positive and Gram-negative bacteria attain a negative charge as they contain teichoic acids and lipopolysaccharides, respectively on their surfaces; they also contained negatively charged phospholipids. As antimicrobial peptide has a net positive charge, it binds to the negatively charged outer surface of bacteria. The lysis of bacterial cells occurs due to the following two processes: (i) the peptide lyses the bacterial membrane by pore formation which results in transmembrane electrochemical gradient damage that leads to loss of energy and ultimately further leads to cell swelling and osmosis (Mulero et al. 2008; Peng et al. 2012b; Masso-Silva and Diamond 2014) and (ii) the peptide act as a multi-hit mechanism, which includes more than one anionic targets (Shai 2002).

The piscidin peptide forms toroidal pores in the membrane as it interacts with acidic phospholipids (Pan et al. 2008; Bae et al. 2014). Their anti-fungal and anti-tumor activity occurs through pore formation, membrane permeabilization and by inducing Reactive Oxygen Species (ROS) and apoptotic pathways (Ebbensgaard et al. 2015; Pan et al. 2007; Dezfuli et al. 2011; Meloni et al. 2015). The peptide has a direct defense mechanism against a wide range of pathogens (Katzenback 2015). The disruption of cell membrane depends on the membrane composition, for example piscidin 1 and 3 by the formation of parallel α helical membrane, they induce a membrane antimicrobial interaction (Masso-Silva and Diamond 2014). The mode of action was through permeabilizing the plasma membrane of the pathogen (Campoverde et al. 2017). The piscidin peptide binds on the bacterial surface based on charge and formed toroidal formation as their mode of action depicted in Fig. 2.

AMPs are interacting as a direct antibacterial mechanism that leads to membrane perturbation, disruption of membrane-associated physiological events to interact with cytoplasmic targets. The positively charged AMP interact with negatively charged lipids in the outer cytoplasmic membrane. The alteration in membrane structure and localized perturbation results in the reorientation of peptide molecules. The peptides diffuse into the cytoplasm through the membrane and reach intracellular targets. The physicochemical and structural characteristic features depend on the interaction of AMPs with membrane (Fjell et al. 2012). The mechanism of piscidin peptide suggests that it targets bacterial and fungal membranes; the replacement of Pro for Gly exhibited bacterial cell selectivity. Pro gives a bent structure in two helices which are for bacterial cell selectivity (Jeong et al. 2016). Also, piscidin functions as an anti-bacterial activity which interacts with acidic phospholipids, thus formed toroidal pores in the membrane (Katzenback 2015).

Piscidin exhibits an antimicrobial activity by forming toroidal pores in bacterial membrane like that of cationic AMPs involved in permeabilization (Mehrnejad and Zarei 2010). The binding and disrupting properties of piscidin 1 and 3 helps in translocation of bacterial cell membranes and attach to the target sites as the mechanism of cell death. The physicochemical properties including cationic, amphipathicity, number of cationic residues and histidine present in

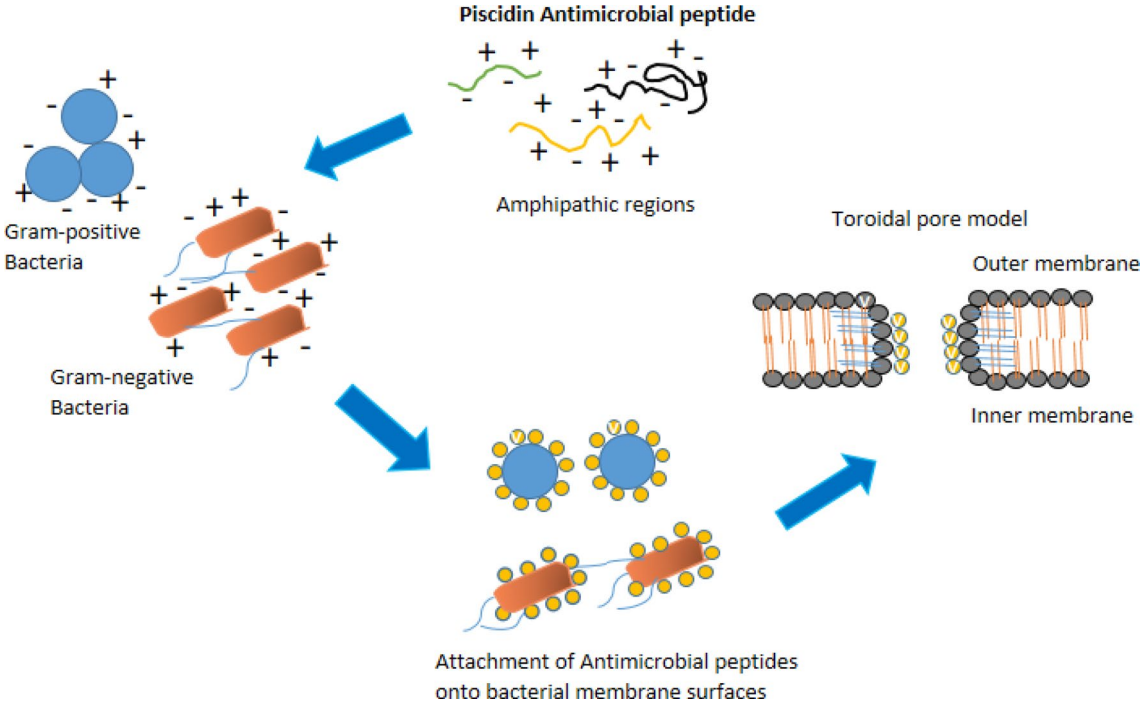

Fig. 2 The mechanism of action of piscidin peptides. The antimicrobial peptide interacts with Gram-positive and Gram-negative bacteria through toroidal pore formation. Due to the presence of biological membranes the peptides fold to form amphipathic structures

piscidin 1 and 3 help in translocating across membranes and synthesis of macromolecules (Hayden et al. 2015).

Other Properties of Piscidin

Piscidins showed antibacterial, antifungal and antiviral properties (Ii, 2007; Dezfuli et al. 2010); recently it was found to have anti-parasitic properties (Colorni et al. 2008). Along with antimicrobial activity, piscidin has anti-tumor activity against cancer-derived cell lines including A549, U937, HT1080,U937, HeLa, HL60,MDA-MB-468, SKBR3, MCF7, T47-D, MDA-MB-231, MCF7-TX400 (paclitaxel-resistant MCF7) and 4T1 (Masso-Silva and Diamond 2014). Piscidins are hemolytic than magainin 2 (Hicks et al. 2003) and less hemolytic than mellitin (Moon et al. 2007). Piscidin 1 can be used as anticancer drug by modifying their sequence form so that other mammalian cells do not damage. The single or multiple modifications in their amino acid sequence may lead to the reduction in hydrophobicity, amphipathicity and helicity, which help to reduce hemolytic action (Lin et al. 2012). Piscidin 1 shown HIV inhibition activity which suggests the importance of cationic arginine side chain. It also shows anti-cancer properties against HeLa and HT1080 cells. Piscidin 2 also has a similar kind of antimicrobial properties (Chen and Cotten 2014).

Among piscidins, piscidin 3 was the least hemolytic peptide (Park et al. 2011). The cytotoxicity and antimicrobial activity increase with the hydrophobicity of peptides (Jeong et al. 2016) and which can be reduced by replacing with positively charged amino acids such as lysine. Piscidin 1 is highly cytotoxic due to the presence of hydrophobic amino acids. Comparatively, piscidin 3 has weaker antimicrobial activity than piscidin 1 and 2 (Colorni et al. 2008). When we compare the peptide treated with untreated samples, the protoplast cell wall was regenerated in treated samples. The antifungal property of piscidin 2 is due to the interaction of the peptide with plasma membrane rather than cell wall, which suggests that peptide act on plasma membrane of *Candida albicans* for exhibiting fungicidal activity (Sung et al. 2008). Piscidin 2 was non-hemolytic against both sheep and human erythrocytes at a concentration lesser than 2.5 μM (Campagna et al. 2007). Piscidin 4 exhibits less hemolytic activity than piscidin 1 in which the C-terminal region prevents the insertion into hydrophobic erythrocyte membrane (Lee et al. 2007).

Therapeutic Applications

The AMPs are most important in pharmaceutics as they are not as resistant as antibiotics. It is involved in chemotaxis, wound healing and can also be used against cancer (Li et al.

2012). At present, the AMPs are the therapeutically important compound with low toxicity and high efficacy in treating bacterial pathogens (Schuerholz et al. 2012). Piscidin 2 disrupts the fungal membrane (Rajanbabu and Chen 2011) and exhibits antifungal activity against human pathogenic fungi (Rakers et al. 2013). This fungicidal properties against *C. albicans*, *Malassezia furfur* and *Trichosporon beigelii* are at MIC values of 1.25–6.25 µM. The antimicrobial activities of piscidin 1 and 2 were found against Gram-positive and Gram-negative bacteria at 0.04–10 µM concentration. These were also found active against *Tetrahymena pyriformes* with PC_{min} value of 1.25 µM. These peptides were potent against *V. vulnificus*, *V. alginolyticus*, *P. aeruginosa*, *S. agalactiae* 819 and *S. agalactiae* BCRC 10787 strains (Peng et al. 2012b). The piscidin derived from tilapia can be used for wound healing due to bacterial infection. Piscidin AMPs showed activity against 11 strains of *Acinetobacter baumanni* and 6 strains of *P. aeruginosa;* and shows low hemolytic activity with human red blood (Jiang et al. 2014). Piscidin showed inhibitory activity against porcine epidemic diarrhea virus (PEDV), pseudorabies virus (PRV), transmissible gastroenteritis virus (TGEV), porcine reproductive and respiratory syndrome virus (PRRSV) and rotavirus (RV) (Hu et al. 2019). Piscidins can be used instead of antibiotics which has no immunotoxic effect (Huang et al. 2015). There is a high demand for AMPs in the food industry to invent the effectiveness of some of the inhibitory compounds, hence these can be used as potential food preservatives too (Li et al. 2012).

Conclusions

The AMPs have great importance in fish as well as human environments as the resistance of different bacterial and other organisms are very common. Day by day the antibiotic resistance is increasing which leads to the necessity of derived AMPs from natural resources. The piscidin peptides from a lower vertebrate group have both commercial as well as medicinal importance. The details related to the structure, classes, gene expression, mechanism and therapeutical importance discussed in this review provided a way to consider its importance in aquaculture industry as well as for human purpose. Apart from the antimicrobial nature of piscidin peptide, it can also be used as an anti-neuropathic, anti-nociceptive, anti-endotoxic and anesthetic compound. Furthermore, there is a need to have research on its designing for the large-scale therapeutics approach. So that, these peptides in humans as well as in aquaculture organisms play a variety of application roles.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest.

Research Involving Human and Animal Rights No human sample or animal sample used in this study.

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