International Journal of Peptide Research and Therapeutics (2022) 28: 153
https://doi.org/10.1007/s10989-022-10459-1

Shrimp Antimicrobial Peptides: A Multitude of Possibilities

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Accepted: 2 September 2022 / Published online: 13 September 2022

Abstract
Antimicrobial peptides (AMPs) are small peptides playing a lead role in the innate immune system of organisms. Marine organisms have a plethora of AMPs that have been widely explored due to their multitude of functions. This review focuses on shrimp derived AMPs and details their versatile nature from an application perspective. It highlights the applications of shrimp AMPs, such as their role in stress regulation and ontogeny, as alternative sexually transmitted diseases drugs, anti-cancer agents, immunomodulators, and biomarkers. Ultimately, we are trying to emphasize that shrimp AMPs are beyond mere antimicrobials.

Keywords Anti-lipopolysaccharide factor · Antimicrobial peptides · Aquaculture · Crustin · Penaeidin · Shrimp

Introduction

Shrimp farming is one of the fastest-growing sectors of aquaculture, which has drawn global attention due to its broad scope in employment, food sector, and its inevitable contribution to the national economy of developing countries by contributing to the overall reduction of world's poverty (Béné et al. 2015). The rampant antimicrobial resistance (AMR) and environmental damages associated with it has put the minds of researchers in agony (Páez-Osuna 2001; Primavera 1997; Thornber et al. 2020). In the recent past, we can see a shift in the trend of global shrimp production from wild captured shrimps to cultured shrimps. Of the worldwide shrimp production in 2016, farmed shrimps contributed to 67%, and the rest by wild-caught shrimps. *Penaeus vannamei* (White leg shrimp) and *Penaeus monodon* (Giant tiger prawn) make up the majority of the species (FAO 2016). Among the various challenges in shrimp aquaculture, AMR is on the verge of destroying the whole aquaculture industry and should be handled immediately to save the aquaculture sector (Thornber et al. 2020).

AMPs are small peptides, mostly amphipathic and are essential components of the innate immunity of organisms. They were initially considered as the controllers of immune response in organisms that lacked adaptive immunity. But later they were found ubiquitous in all organisms with a complex immune system (Hancock 2006; Nguyen et al. 2011). The antibacterial property of AMP is due to the interaction between positively charged peptides with the negatively charged bacterial membranes, forming pores on them (Yeaman and Yount 2003). Exploration of shrimp AMPs was initially carried out to study the antibacterial potency. The scope of AMPs has outreached mere antibacterial activity to various multidimensional aspects. AMPs from shrimp combines the benefits of immunomodulators, stress regulators, anti-viral agents and anti-tumour agents (Chen et al. 2019; Havanapan et al. 2016; Huang et al. 2015; Sruthy et al. 2019) (Fig. 1). AMPs potentially evolve significantly less resistance in microbes, making them stand out from the antibiotics (Spohn et al. 2019). Penaeidin, crustin, stylicin, anti-lipopolysaccharide factors (ALFs), histone-derived AMPs, and haemocyanin-derived AMPs are among the shrimp AMPs listed to date.

Penaeidins, crustins, and ALFs make up the cationic AMPs in penaeid shrimps, which come in a variety of classes or isoforms and have antibacterial and antifungal properties against various types of bacteria and fungi. Penaeidins, a unique AMP family said to be found only

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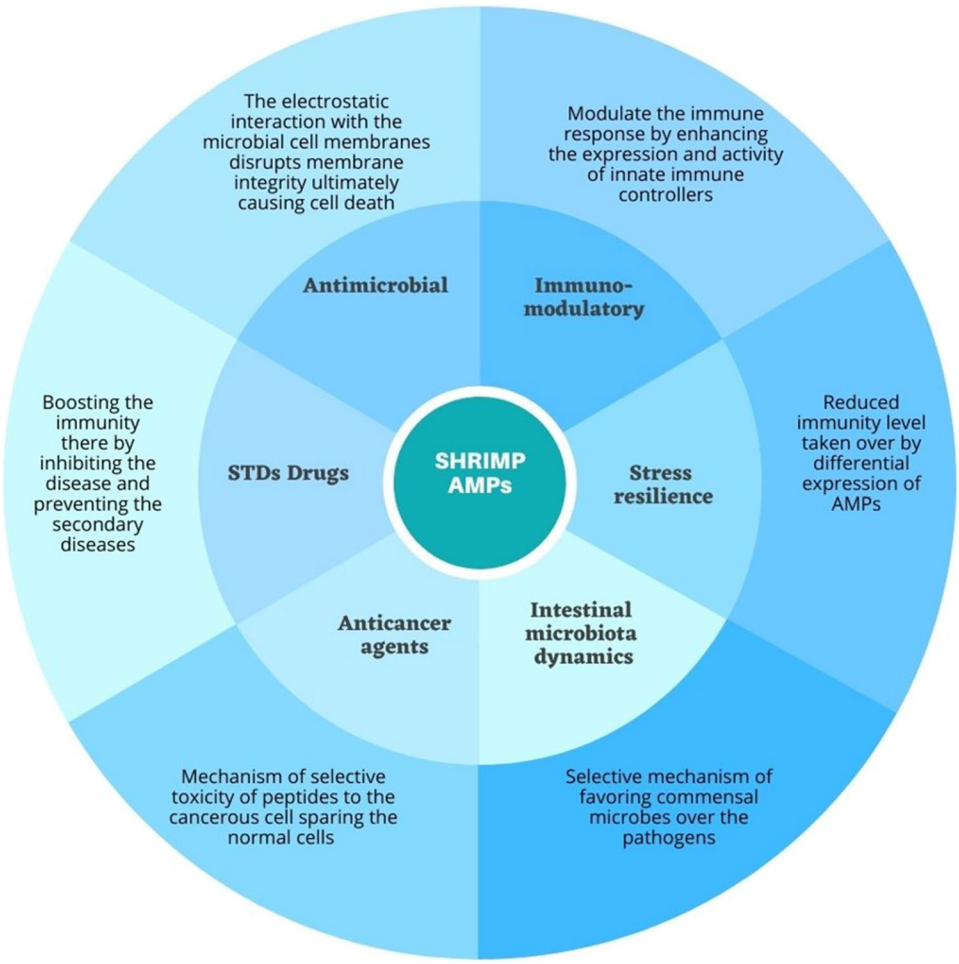

Fig. 1 The multi-dimensional applications of shrimp AMPs

in penaeid shrimp, are distinguished by two unique active domains: a proline-rich N-terminal region and a cysteine-rich C-terminal domain with six cysteine residues. The antibacterial and chitin-binding activities are relied upon the six cysteine-rich motifs in the C-terminal region (Bachère et al. 2000; Destoumieux et al. 2000a). Cationic cysteine-rich AMPs present in crustaceans with a single whey acidic protein domain at the C-terminus are crustins (Smith et al. 2008). ALFs are a large and diverse family of proteins found in shrimp. There are five different subgroups of ALFs: ALF-A, which includes anionic and cationic polypeptides of 11.4–11.5 kDa, ALF-B groups includes cationic polypeptides of 10.6–11.2 kDa, ALF-C cationic polypeptides of 11–11.3 kDa, and ALF-D anionic polypeptides of 10.7–10.8 kDa, ALF- E anionic and cationic polypeptides of 11.4–12.5 kDa (Jiang et al. 2015; Rosa et al. 2013). Stylicins are 8.9 kDa multi-domain anionic (pI5) peptides that are identified in penaeid shrimps. They consist of a proline/arginine-rich N-terminal domain followed by a 13 cysteine residue C-terminal domain (Rolland et al. 2010). The C-terminus of respiratory proteins haemocyanins present in penaeid shrimps are found to release anti-fungal peptides (Destoumieux et al. 2001). The histidine-rich AMP released by crustacean haemocyanins are found to selectively bind to the fungal cell wall by adopting an amphipathic alpha helical structure and permeabilize fungal membranes (Nakamura et al. 1988).

Understanding the versatile applications of shrimp derived AMPs in various sectors can be a better approach in reducing the AMR dissemination and a step towards sustainable aquaculture development. Bioinformatic techniques are trending in AMP research to predict the potentiality of peptides and have kept the high cost of production and futile work at bay. This review enlists the recent shrimp derived AMPs with their potential applications categorized as anti-bacterial and anti-biofilm agents, anti-fungal and anti-protozoan AMPs, AMPs as immunomodulators, AMPs in stress resilience, anti-cancerous property of AMPs, AMPs as alternative drugs for STDs treatment and the ontogenetic applications. The present review outlines several applications of shrimp derived AMPs for an improved understanding of various potential peptides discovered from shrimp during the past decade that can be leveraged into promising drugs.

Antibacterial and Antibiofilm Agents

The role of shrimp AMPs in antibacterial activity have been widely studied, and various shrimp derived peptides are discovered against both Gram-positive and Gram-negative bacteria. The positively charged AMPs generally show more affinity towards the negatively charged bacterial membranes inducing membrane disruption or can act in non-membrane disruptive mechanism by interrupting the intracellular functions (Huang et al. 2010; Jiang et al. 2008). The most advanced LvBigPEN peptide, derived from *Litopenaeus vannamei*, exhibits notable antibacterial activity against the *Vibrio parahaemolyticus* strains of Gram-negative bacteria with very low minimum inhibitory concentration (MIC). The *V. parahaemolyticus* bacteria that causes "early mortality syndrome" (EMS) is explicitly proved to be inhibited by the LvBigPEN peptide that binds the DNA and membranal components of the bacteria (Xiao et al. 2021). Since many articles have been published on the antibacterial application of AMPs, we focus our attention on applications other than antibacterial. Some of the recent antibacterial peptides of shrimp are listed for reference (Table 1).

Bacterial species make biofilms to become more resistant to conventional antibiotics (Sharma et al. 2019). Biofilms are a collection of numerous microorganisms found along with slimy extracellular polymer substance (EPS). Stress factors such as pH variation, atmospheric variations, antibiotics, host immune system, nutrient deprivation causes the microorganisms to produce biofilm components as an adaptation. Biofilm comprises of DNA, proteins, lipids, water and polysaccharides (Attaran and Falsafi 2017; De la Fuente-Núñez et al. 2014, 2016; Flemming et al. 2016; Pletzer and Hancock 2016). Well, a cell that switches to the biofilm mode triggers a stringent response, that is, a stress control mechanism seen in both Gram-positive and Gram-negative bacteria, signalled by the alarmone nucleotide (p)ppGpp (De la Fuente-Núñez et al. 2014; Pletzer and Hancock 2016). A study about the mechanism of AMPs antibiofilm activity revealed that peptides can interact with the signalling nucleotide, (p) ppGpp. The peptide binding leads to ppGpp degradation and thereby blocks the stringent control, which leads to biofilm prevention or eradication/dispersal of preformed biofilm. For understanding in detail, the mechanism of biofilm inhibition by AMPs, the reader is referred to read (Raheem and Straus 2019).

Biofilm based novel immunostimulants are used for high-health pacific white shrimp, *P. vannamei* farming. The implications of the oral administration of inactivated biofilm cells of *V. harveyi* embedded on a chitin substrate was that the biofilm-based immunostimulants effectively triggered an immune response through the expression of antigenic proteins and AMPs. Peptides such as penaeidin, crustin and lysozyme impacted the immune response bringing improved growth, survival and health status of the shrimp (Vinay et al. 2019). A recent example described a bio peptide (crustin) isolated from *P. semisulcatus* that exhibited an effective resistance to Gram-positive bacteria *Bacillus thuringiensis* and *B. pumilis* and was also influential in complete inhibition of biofilm formation at a concentration of 40 µg/ml (Sivakamavalli et al. 2020). Haemocyanin derived peptide, a component of innate immunity with a wide range of antimicrobial activity, was also found to be potential in biofilm inhibition. The peptide displayed antibacterial activity against both Gram-positive and Gram-negative bacteria and exhibited high efficiency of inhibition at 100 µg/ml concentration. Also, the peptide minimized the viability of the bacterial cells (Ishwarya et al. 2020).

Antifungal and Antiprotozoal Applications

AMPs act on fungi and protozoans through membrane interactions or intercellular targets (Matejuk et al. 2010). Fungal diseases frequently hit the shrimp industry, even then minimal studies had done on shrimp derived antifungal peptides and very few on antiprotozoal peptides. And recently, fungal diseases and protozoan parasites are causing much trouble to humankind, causing hard-to-heal diseases such as black fungus and white fungus, wreaking havoc and killing thousands of people. Future research recommends more work in this application to fill the information gap and combat the short availability of antifungal and anti- protozoan drugs.

A tropical protozoan disease caused by *Trypanosoma cruzi* called Chagas disease characterized by swelling and fever seen to cause congestive heart failure when left untreated (Pittella 2009). Peptides Hmc666-678 and Hmc364-382 outperform benznidazole (BZ), a drug in use to treat Chagas disease, with a selective index > 50 and 77 times lower half-maximal inhibitory concentration (IC50) of BZ for the trypomastigote form (Monteiro et al. 2020). Interestingly *F. oxysporum,* a pathogen of penaeid shrimp when treated with PvHCt, got permeabilized by the α-helical structure adopted by the peptide. However, the peptide has failed to adopt the α-helical system in fully anionic SDS micelle of bacterial membrane showing its specificity towards fungal membranes (Petit et al. 2015). Fusariosis is an opportunistic fungal disease caused by *F. solani*, which causes melanization of the gill and locomotory difficulties due to mycelial growth. The fungus infection showed differential expression of AMP genes such as Farpau ALF-B and Fpau-Stylicin2 with an upregulated expression with the progression of the illness. The mechanism of action of peptides

Table 1 Applications of various shrimp derived AMPs

Peptide	Source	Characteristics	Mechanism of action	Application/Activity	References
Antibiofilm and antibacterial					
Haemocyanin derived peptides	*Peneaus semisulcatus*	Crystalline homogenic peptide, β-sheet 2^0 structure	Protein–ligand interaction	*Bacillus thuringiensis, B. pumilis, Vibrio alginolyticus, V. parahaemolyticus* bacteria	Ishwarya et al. (2020)
Crustin	*Peneaus semisulcatus*	α-helices with random coils as 2^0 structure	Bacterial agglutination and cell membrane permeabilization	*B. thuringiensis* and *B. pumilis antibiofilm*	Sivakamavalli et al. (2020)
LBD8	*Fenneropenaeus chinensis*	Conserved cysteine residues at either ends of the domain determine the antibacterial activity	Interaction of basic aminoacids and cationic components with bacterial membranes	*Vibrio* sp	Li et al. (2019)
MjPen-II	*Marsupenaeus japonicus*	N-terminal proline-rich region (PRR), C-terminal cysteine-rich region (CRR) containing six cysteine residues that forms three disulfide bonds and a serine rich region	Phagocytosis	Gram-negative bacteria, namely *E. coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, V. anguillarum* and three of the Gram-positive bacteria, *B. megaterium, B. subtilis, Staphylococcus aureus*	An et al. (2016)
Mjthymosin3	*Marsupenaeus japonicus*	Actin-binding peptide	Mediate external clearance of bacteria	*E. coli* and *V. anguillarum*	Feng et al. (2019)
Antiviral					
Cyclic shrimp ALF (cSALF)	*Penaeus monodon*	β-hairpin structure stabilized by disulfide bridge interacts with the LPS acyl chains	Agglutination of virions	Nervous necrosis virus	Chia et al. (2010)
PEN 2	*Litopenaeus vannamei*	Variant of PEN1 with 53aa	Disrupting immunoglobin receptor attachment	White spot syndrome virus	Xiao et al. (2020)
BigPEN	*Litopenaeus vannamei*	Contains an additional repeat region to the PEN domain	Blocking the viral entry	White spot syndrome virus	Xiao et al. (2020)
LvSWD3	*Litopenaeus vannamei*	Single WAP domain peptide	Modulation of gene (Dorsal, STAT and IRF)	White spot syndrome virus	Yang et al. (2018)
Mj-sty	*Marsupenaeus japonicus*	13 cysteine residues with a PRR and a CRR region	Not specified	White spot syndrome virus	Liu et al. (2015)
LvHcL48	*Litopenaeus vannamei*	79 aa in the C-terminal domain of the hemocyanin protein	Interaction with WSSV envelop protein	White spot syndrome virus	Zhan et al. (2019)
Anti fungal and anti protozoan					
Hmc666-678 and Hmc364-382	*Penaeus monodon*	β-sheet and α-helix/α-helix respectively	Cell death by necrosis	*Trypanosoma cruzi*	Moteiro et al. 2020
PvHCt	*Litopenaeus vannamei*	Histidine rich AMP that adopts an amphipathic α-helical structure	Permeabilization of fungal cells	*Fusarium oxysporum*	Petit et al. 2016)
Farpau ALF-B and Fpau-Stylicin2	*Farfantepenaeus paulensis*	Cysteine residues stabilize β-hairpin structure	Not specified	*Fusarium solani*	Machado et al. (2021)

Table 1 (continued)

Peptide	Source	Characteristics	Mechanism of action	Application/Activity	References
SALF	*Penaeus monodon*	Three α-helices packed against a four-stranded β-sheet	Modulation of proinflammatory cytokines through the p38 and NF-κB pathways	*Trichomonas vaginalis*	Lin et al. (2012)
H2B, H3, H4	*Litopenaeus vannamei*	Histone derived peptides	Increased expression of antimicrobial peptides	Cold stress	Fan et al. (2019)
ALF-6	*Penaeus monodon*	Possess eight negative and 13 positively charged residues	Modulators of immune function	Ammonia stress	Li et al. (2018)
Anticancer					
LvHemB1	*Litopenaeus vannamei*	Cationic AMP with 15 aa and amphipathic α-helical structure	Target VDAC1, mitochondrial dysfunction, apoptosis	Human cervical (HeLa), hepatocellular (HepG2), esophageal (EC109), and bladder (EJ) cell lines	Liu et al. (2021)
SALF	*Penaeus monodon*	Three α-helices packed against a four-stranded β-sheet	Caspase dependent apoptosis	HeLa cells	Lin et al. (2010)
Peptide B11	*Litopenaeus vannamei*	Haemocyanin derived peptide	Mitochondrial-dependent apoptosis	HeLa, HepG2, EC109	Liu et al. (2018)
Fi-Histin	*Fenneropenaeus indicus*	Histone H2A derived peptide with a predicted α-helical 2° structure	Mitochondrial-dependent apoptosis	Lung cancer cell lines (NCI–H460) and pharyngeal cancer (HEp-2) cells	Sruthy et al. (2019)
SALF	*Penaeus monodon*	Three α-helices packed against a four-stranded β-sheet	As vaccine adjuvant, immunomodulation	Murine bladder carcinoma cells (MBT-2)	Huang et al. (2010)
HMC	*Litopenaeus vannamei*	Haemocyanin derived peptide	Mitochondrial-dependent apoptosis	HeLa cells	Zheng et al. (2016)
STDS					
$csSALF_{55–76}$ & $lsSALF_{55–76}$	*Penaeus monodon*	Synthetic ALF	Lytic activity of the peptide on cell or nuclear membrane	*Propionibacterium acnes* and *Trichomonas vaginalis*	Pan et al. (2009)
SALF	*Penaeus monodon*	Three α-helices packed against a four-stranded β-sheet	Reducing the production of proinflammatory cytokine	*Trichomonas vaginalis*	Lin et al. (2012)
Immunomodulatory					
Penaeidin	*Penaeus monodon*	N-terminal proline-rich domain and a C-terminal cysteine-rich domain	Integrin-b-mediated cytokine feature that promotes shrimp granulocyte and semi-granulocyte adhesion	Cytokine	Li and Song 2010)
SALF	*Penaeus monodon*	Three α-helices packed against a four-stranded β-sheet	Enhanced production of T-helper cells, macrophages and natural killer	Adjuvant	Huang et al. (2015)
SALF	*Penaeus monodon*	Three α-helices packed against a four-stranded β-sheet	Down-regulation of proinflammatory cytokine	Cytokine modulation	Lin et al. (2012)
Miscellaneous applications					

Table 1 (continued)

Peptide	Source	Characteristics	Mechanism of action	Application/Activity	References
LvCrustinI-1	*Litopenaeus vannamei*	173 aa long single peptide, cysteine and glycine rich region	Binding the microorganism	Intestinal homeostasis	Lv et al. (2020)
Re-crustin	*Rimicaris exoculate (symbiotic shrimp)*	Type-I crustin with a glycerin rich region followed by a C-terminus containing four conserved cysteine residues and a WAP domain	Ectosymbioses establishment	Ectosymbioses	Lv et al. (2020)
Penaeidin 3–2	*Fenneropenaeus chinensis*	N-terminal proline-rich domain and a C-terminal cysteine-rich domain	Changing the bacterial community of intestine	Feed	Liu et al. (2014)
ALF, penaeidin and stylicin	*Penaeus monodon*	-	*Vibrio parahaemolyticus* AHPND strain (VpAHPND) infection	Biomarker	Chiew et al. (2019)

Farpau ALF-B and Fpau-Stylicin2 are yet to be explored in detail, but proved to be inhibiting *F. solani* (Machado et al. 2021). *Trichomonas vaginalis*, another parasitic protozoan, generally infects the male and female reproductive tract accompanied by a sensation of burning, itching, and inflammation, seldom making them prone to human immunodeficiency virus (HIV) type-1 infection (Kissinger et al. 2008). The role of shrimp anti-lipopolysaccharide factor (SALF) in inhibiting *T. vaginalis* has been studied in detail to elucidate the mechanism behind the resistance and concluded that the decreased expression of pro-inflammatory cytokines (tumour necrosis factor (TNF)- α, interleukin (IL)-1 α, IL-6, IL-8, and monocyte chemoattractant protein (MCP)-1) mediated it. In addition, the peptide blocks the interaction between a parasite's adhesion protein AP65 with the cell membrane (Pan et al. 2009; Lin et al. 2012).

Antiviral Peptides

Rather than terrestrial agriculture, aquaculture is more prone to virus attacks than terrestrial agriculture due to the raised stock densities accompanied by stress levels in shrimp farms. The strained environment could facilitate more rapid infestation and multiplication of the viruses (Kibenge 2019). Viral diseases account for a significant share of infectious diseases in shrimp aquaculture, while viral chemotherapies are not updated comparatively with the rising cases of viral infections. Examples of the most prevalent viral diseases in shrimp aquaculture are White spot syndrome (WSSV), Monodon Baculovirus (MBV), Infectious hypodermal and haematopoietic Necrosis Virus (IHHNV), Hepatopancreatic Parvo-like Virus (HPV) (Kibenge 2019). The emergence and prevalence of varied contagious viral diseases brought about a pressing need for finding a solution to these diseases.

Antiviral peptides (AVP) act by effectively targeting and interacting with viral envelopes, viral sub-particles, thereby preventing viral entry, and also through modulation of immune responses (Ahmed et al. 2021). Besides a pre-treatment strategy, AVPs are modulators of immune responses in post-viral infectious conditions. Nervous necrosis virus (NNV), a virus that causes abnormal swimming patterns and brain and eye vacuolation in fishes spotted to get clumped by cyclic shrimp anti-lipopolysaccharide factor (cSALF) in a study carried out in grouper fin and barramundi brain cell lines. The study suggested that the hydrophilic to hydrophobic transformation caused by the cSALF to the capsid proteins irreversibly agglutinate the virion instead of regulating immune responses, (Chia et al. 2010) whereas, in *Marsupenaeus japonicus*, Mj-sty displayed modulation of immune functions post-WSSV infection (Liu 2015).

The antimicrobial parts of the peptide LvSWD3, a single whey acidic domain (SWD) holder peptide, seemed

to be viral specific wherein the peptide has decelerated the mortality rates in WSSV infected white shrimp and also aided in reducing the viral load in the tissues (Yang et al. 2018). Most recently, a WSSV challenged *L. vannamei* produced an 8.9 kDa peptide named LvHcL48. It has significantly reduced the transcript level of wsv069 and wsv421 viral genes in the haemocytes of shrimp both in vivo and in vitro treatment. The underpinning mechanism of the inhibition was deduced to be its interaction with WSSV envelop protein VP28 (Zhan et al. 2019). In line with this, Xiao et al. (2020) also reported that the binding of penaeidin peptide PEN 2 with VP24 caused the release of viral particles from the polymeric immunoglobulin receptors needed for the infection. Another unique penaeidin peptide BigPEN interferes with viral protein VP28 viral interaction with Rab7 – the Rab GTPase that mediates the viral entry. Li et al. (2015) stated that LBD peptides of FcALFs (*Fenneropenaeus chinensis*) inhibit WSSV replication, and lysine residues replacement with other amino acids affected the antiviral property of LBD peptides. Consistent with this report, the interaction of ALFPm3 peptide with the complex structural proteins of WSSV distorted the viral proteins' integrity, thereby preventing the attachment and acting as a solid antiviral agent (Methatham et al. 2017).

Role of AMPs in Shrimp Ontogenesis

Antimicrobial peptides and the modulation of these peptides in relation to ontogeny was a much-preferred area of research that later shifted onto its other applications. Ontogeny studies are indispensable for shrimp aquaculture as both the hatchery techniques and culture processes need to be checked and appropriately regulated for the industry's success. Various stressors affect the shrimp juveniles and larvae, such as abiotic factors, pathogenic microbes and infectious diseases (Dall et al. 1990). The circulating haemocytes with various immune factors like AMPs are sole immune regulators during the developmental stages (Tassanakajon et al. 2013). Several peptides from shrimp have been detected in synergy with different developmental stages. A few instances that demonstrated the influence of AMPs in various developmental stages were Fc-crus 1 and Fc-crus 2, expressed in the early developmental stages of *F. chinensis* (nauplii, mysis, and post-larvae). Indeed, Fc-crus 3 was exclusively detected from ovaries of adult shrimps, suggesting that it may be aiding ovary development (Sun et al. 2010). Another study demonstrated the expression of crustin-like *Lv* gene in all stages of development of *L. vannamei* and also seen in the fertilized eggs in 7–11 h post-spawning stage given the cue to the maternal contribution of immune transcripts to the progeny. The early expression of AMPs in the developmental stages hint towards the critical role played by AMPs in immune regulation in the absence of a fully flourished immune system and the role of AMPs in building the natural microbiota that aids the premature immune system of shrimp (Barreto et al. 2018). Quispe et al. (2016) substantiate the maternal contribution of immune genes in a study and detected the traces of AMPs such as Litvan PEN1/2, Litvan PEN4, Litvan ALF-A, Litvan ALF-D and Litvan ALF- B in the nauplius and protozoea stages with an eventually increased expression in the developmental stages. The expression profile of stylicin peptide Mj-sty hint at the role of AMPs in the metamorphosis of shrimp. It was noted that the peptide had been transcribed throughout the developmental stages with significant differences in the pattern of expression, showing that the peptide plays a significant role in the immunity and metamorphosis of shrimp larvae (Liu et al. 2015).

Anticancer Agents

Despite the significant advances in medical science, cancer is a significant threat to humankind. Recent cancer therapies include chemotherapy, endocrine therapies, surgery, radiotherapy and similar treatments. Metastatic cancer treatment still resorts to conventional chemotherapy, where the major challenge is drug resistance (Housman et al. 2014; Miller et al. 2016). Studies on the anticancer properties of shrimp AMPs revealed several potential drug candidates and demanded proper prior trials and researches before commercial usage. A cationic antimicrobial peptide LvHemB1, a haemocyanin gene derived from *L. vannamei*, has been shown to efficiently decrease the cell viability of the human cervical (HeLa), hepatocellular (HepG2), oesophageal (EC109), and bladder (EJ) cancer cells by 70.30%, 53.26%, 49.01%, 78.44% respectively at 24 h treatment (Liu et al. 2021). The defining trait to be considered anti-cancerous peptide (ACP) is killing cancer cells, sparing the normal cells selectively. Differences in the membrane interaction of the cancer cells with the ACP accounted for this selective toxicity (Hilchie et al. 2019). The net negative charged nature of the cancer cells due to the overexpression anionic molecules such as phosphatidylserine (PS) attracts the cationic AMPs (Hoskin and Ramamoorthy 2008; Utsugi et al. 1991). A recent report says cervical cancer is the most common death cause for women in 55 countries (Bray et al. 2012). Cisplatin, an antitumour agent, widely used for cervical cancer treatment, upshot deleterious outcomes: intrinsic and acquired drug resistance and toxicity (Siddik 2003). Interestingly, when cisplatin-treated in combination with SALF, an enhanced effect was reported than its solitary usage. SALF is non-toxic to normal cells, administrated in cooperation with cisplatin (in vitro), has shown a maximum tumour growth inhibition compared to 10 µM

cisplatin treatment alone (Lin et al. 2010). Furthermore, SALF is an efficient peptide as a cancer vaccine adjuvant in treating bladder tumours. Co-treatment with inactivated murine bladder carcinoma cells MBT-2 Lysate promoted innate IL-1β production in mice macrophages, indicating an enhanced immunity (Huang et al. 2015). Haemocyanin caused the up-regulation of 10 apoptosis-associated proteins suggesting it as a potential peptide triggering mitochondria-dependent apoptosis. In contrast, another peptide, B11, an in silico predicted protein designed from the hemocyanin of shrimp *L. vannamei* caused the loss of mitochondria membrane potential, resulting in mitochondrial-dependent apoptosis (Liu et al. 2018; Zheng et al. 2016). In addition, Fi-Histin, a histone derived AMP, from *Fenneropenaeus indicus* displayed anticancer activity against lung cancer cell lines (NCI–H460) and pharyngeal cancer cell lines (HEp-2). In vitro analysis results briefed that the up-regulated expression of cancer controlling genes (Bax, Caspase 3, Caspase 9 and Rb1) and cytokine related immune genes mediated anticancer activity (Sruthy et al. 2019).

Intestinal Microbiota and AMPs

The gut microbiome is a dynamic microbial community that works naturally with the body in a mutualistic way shaping the host immunity (Moossavi and Bishehsari 2019). It comprises different viruses, bacteria, and fungi, producing molecular metabolites that benefit the host (Chen et al. 2018; Focà et al. 2015). Recently the trend of amping up the gut microbiome for better health of the organisms has been widespread. Cullen et al. (2015) explained the mechanism by which the AMPs selectively aids the commensal microbiome growth while inhibiting the pathogens. The commensal microbes produce a particular enzyme (LpxF) capable of dephosphorylating the lipid A portion of lipopolysaccharide (LPS). This action results in reduced expression of negatively charged components on the cell membrane, thereby displaying less affinity towards the cationic AMPs. AMPs regulate the gut microbiome either through direct antibacterial activity or by modulating the immune functions in the intestinal environment (Bevins and Salzman 2011). Microbial dysbiosis can negatively affect immunological processes, and any dysregulation in AMP production can exacerbate the conditions leading to many diseases.

It was recently reported that stylicins from *L. vannamei* named *Lvan*-Stylicins was produced in response to *Vibrio* infections in the midgut columnar epithelial cells. The peptide displayed pronounced expression in the anterior caecum region of the midgut, where a cuticular layer is absent, giving the insight that AMPs can act as the first line of defence. Continued study on the peptide revealed that it responded to the homogenate of WSSV infected shrimp muscle but were not displaying any modulation on WSSV challenge, suggesting the role of the peptide in earlier wound healing and inflammation processes (Farias et al. 2019). Indeed, two genes of study (LitvanALF-A and LitvanALF-C) displayed no modulation in expression during *Vibrio* infection indicative of the microbe-associated molecular patterns (MAMP) triggered gene expression instead of tissue damage (Silveira et al. 2018). Another study demonstrated PmALF7, an ALF isoform expression on the stomach during Acute Hepatopancreatic Necrosis Disease (AHPND). *V. parahaemolyticus,* the pathogenic strain causing AHPND, colonizes the stomach initially. PmALF7 exhibited upregulated expression for 6 and 12 h post-infection in the stomach and lymphoid organ during *V. parahaemolyticus* strain 3HP (VP3HP) infection (Soonthornchai et al. 2016).

Immunomodulatory Functions of AMPs

Recently the versatile functions of AMPs have been explored with great interest resulting in the characterization and identification of numerous peptides with potentials beyond mere antimicrobial ability. The varied roles of AMPs emphasizing their roles in immune regulations have recoined them as HDPs (Radek and Gallo 2010). Earlier researches interpreted the mechanism of actions of AMPs to be membrane permeabilization. Still, new trends are discovering, such as the control of the internal biochemical processes of microbes and recent finding of their involvement in boosting the host immunity to combat the foreign organisms. Generally, AMPs mediate the immunomodulatory activities by recruiting macrophages and mast cells, inducing chemokine production and modulating the NF-κB signalling pathways (Otvos 2016). Targeting the immune system to treat infectious and deadly diseases is a trending approach in medical research. Recently, researchers have been researching how these peptides work to boost innate immunity to overcome various hard-to-treat diseases. Due to their ability to reduce inflammation and their role in pain modulation, biopeptides are becoming increasingly important in the field of biopharmaceuticals (Monge-Fuentes et al. 2018). Anti-inflammatory action has been demonstrated even in the peptides found in arthropod venom. AMPs are essential for immune control in shrimps since their only defense against intruders are innate immunity (Santos et al. 2021).

Antibacterial peptides from crustaceans with cysteine-rich ends have chitin binding properties that enhance their antimicrobial action and also contribute to their ability to promote wound healing. (Destoumieux et al. 2000a, 2000b). The chitin binding property of AMPs aided the process of molting in penaeid shrimps illustrated by Bachère et al. in the activity of penaeidins (Bachère et al. 2004). Penaeidins

act as pro-inflammatory cytokines through the aggregation of haemocytes to the wound cites (Li and Song 2010). In shrimps, host–pathogen interaction recognized by the Toll and immune deficiency (IMD) pathways activates nuclear factor-κB (NF-κB) and facilitates the release of AMPs (Okumura et al. 2008; Okun et al. 2005; Pan et al. 2009). Li et al. (2010) featured penaeidin with cytokine features that promote an integrin-mediated hemocyte adhesion of granulocyte and semi-granulocyte that exhibited the immunomodulatory function of penaeidin apart from its bactericidal properties. SALF mediates the proinflammatory cytokine expressions in *T. vaginalis* infection, which down-regulated the expression of interleukin (IL)-1α, IL-6, IL-8, MCP-1 and tumour necrosis factor (TNF)- α secreted through the NF-κB and MAPK pathways (Lin et al. 2012). SALF was reported to act as adjuvants in cancer vaccines against bladder associated tumours. Evidence from the enhanced production of T-helper cells, macrophages, and natural killer (NK) cells followed by the vaccine application implied the peptide's potential in secondary tumours suppression (Huang et al. 2015). Another peptide, MjPen-II, with the phagocytic property has been identified to promote bacterial inhibition through agglutination and phagocytosis property (An et al. 2016).

AMPs against STDs

Synthetic peptides of ALF, csSALF$_{55–76}$ and lsSALF$_{55–76}$, of the *P. monodon* species were proven to be effective against *Propionibacterium acnes* and *T. vaginalis* (Pan et al. 2009). *T. vaginalis* infection is one among the frequently hit sexually transmitted diseases that causes itching, burning and inflammation of the vaginal epithelium (Alderete and Garza 1985; Munson et al. 2008). *T. vaginalis* infection increases the vulnerability towards human immunodeficiency virus (HIV) type-1 and cervical cancer (Kissinger et al. 2008; Zhang and Begg 1994). Indeed, shrimp ALF through the down-regulation of proinflammatory cytokines release, inhibits *T. vaginalis*-induced HeLa cells. Proinflammatory cytokines such as TNF- α, IL-1 α, IL-6, IL-8, and MCP-1, secreted by the infected cells are inhibited through the MAPK and NF-kB pathway (Lin et al. 2012). It is to our surprise that bacterial vaginosis increases the risk of associated sexually transmitted diseases whereas vulvovaginal candidiasis has shown much weaker chance. And it was found that, compared to the vaginal fluid from healthy or women with vulvovaginal candidiasis, bacterial vaginosis infected person shows less presence of antimicrobial polypeptides and antimicrobial activity (Valore et al. 2006). Its high time to look for more natural and resistance free drugs as there is a rising tides of debates on how far we can run with the available drugs like azithromycin and metronidazole (Bangura et al. 2021; Okun et al. 2005).

AMPs in Stress Resilience

Stress mitigation in aquaculture has become a growing concern for researchers due to the demand driven growth and associated emergence of diseases in shrimp culture system. Environmental stress triggers the innate immune system of shrimps (Engel and Barton 2010) and also stresses make them susceptible to diseases such as WSSV (He et al. 2000; Chen et al. 2010). AMPs are not only known for its immune properties, but have shown explicit role in stress management. Few of the humoral immune signalling genes are seen to be differentially expressed during environmental stress (Chen and He 2019). Under unfavorable conditions, the Unfolded Protein Response (UPR) trade off unvital proteins for the vital ones causing a decrement in immune factors (Walter and Ron 2011). LvCruU from *L. vannamei*, a novel crustin gene has shown enhanced antibacterial function under ER-stress. The LvCruU gene, a downstream effector of shrimp UPR gets induced by transcription factor 3 (LvATF3) of UPR and compensate for the reduced immune level providing antibacterial protection under UPR activation (Chen et al. 2019). Heavy metal pollution is a growing stress to aquaculture organisms causing stunted growth and increased mortality rates. Furthermore, copper (Cu) stress decreases total hemocyte count (THC), anti-oxidative capacity of the shrimp and increases the vulnerability to *V. alginolyticus* infection (Guo et al. 2017; Qian et al. 2020; Yeh et al. 2004). iTRAQ-based quantitative proteomics profiling of white shrimp *L. vannamei* exposed to copper stress and ammonia stress revealed 385 and 202 differentially expressed proteins (DEPs) wherein ALF and hemocyanin peptides were identified as modulators of immune functions (Guo et al. 2021; Lu et al. 2018). And in *P. monodon* under ammonia stress showed upregulated transcription ALF 6 isoforms (Li et al. 2018). Moreover, cold stress homeostasis involves upregulated expression of histone peptides (H2B, H3, H4), which are known for their antimicrobial activity (Fan et al. 2019; Patat et al. 2004). The evidence of differently expressed Crustin, Penaeidin-2a, and Penaeidin-4a genes in the hepatopancreas of *L. vannamei* under acute ammonia-nitrogen stress merely stemming the fact that AMPs are crucial in stress management (Lu et al. 2016). All these instances hint towards the ability of AMPs to be deployed as biomarkers for stress. The role of AMPs in optimizing stress resilience have to be investigated in detail to bring out possible stress mitigation strategies in aquaculture sectors.

Recent Trends

- AMPs in regulating intestinal microbiota: The applications of AMPs are widening into new grounds like regulating intestinal microbiota homeostasis. A novel crustin LvCrustin I-1 has exhibited microorganism binding property but then failed to show antimicrobial property, is believed to be aiding the intestinal microbiota homeostasis. Subsequently, the LvCrustin I-1 knockdown increased the Demequina and Nautella bacteria, picturized the chaotic unhealthy intestinal environment thereafter (Lv et al. 2020). Intestinal microbiota homeostasis is an indicator of good health as it serves as a "virtual endocrine organ", controlling the host nutrient assimilation and pathogen invasion (Clarke et al. 2014).
- AMPs aiding ectosymbiosis: The symbiotic shrimp *Rimicaris exoculate* has undergone extensive research to understand the hidden theory behind the nature of hosting highly specialized ectosymbiotic community, in its cephalothoracic cavity (Guri et al. 2012; Petersen et al. 2010). Astonishingly, a novel anti-Gram-positive type II crustin (Re-crustin), was identified molecularly from the inner surfaces of the cephalothoracic cavity and its appendages. Extrapolating the spatio-temporal correlation between the Re-crustin production and the ectosymbiosis-related life-cycle events hint towards the potential role of AMP, in the establishment of vital ectosymbioses (Le Bloa et al. 2020). The theme of AMPs and ectosymbiotic relationship was diametrically opposite of the kind of function, mostly AMPs was doing. It is considered as a latent potential of AMPs and there should be more studies to decipher the exact mechanism behind these applications of shrimp AMPs.
- Shrimp AMPs into feedstock industry: Penaeidin 3–2 expressing transgenic rice bran was used to feed Tilapia species. Aside from being a microbe free feed, it has stimulated the micro flora of fish intestine and have shown lesser mortality rates when challenged with *Aeromonas hydrophila.* It was noted that the affected individual fed with the transgenic rice bran maintained an intact intestine structure to the ones not fed with a damaged villi and epithelium of intestine. Moreover, this finding illustrates the wider possibilities of using plant production system for generating AMPs that are difficult to produce with yeast and bacterial systems (Liu et al. 2014).
- Shrimp AMPs as biomarkers for disease: Variations in the AMP level associated with disease has been sensed as a potential biomarker for diseases and infections that would otherwise be difficult to diagnosed easily. Hepatopancreatic level of ALF, penaeidin, and stylicin were found to be substantially increased with *V. parahaemolyticus.* Acute hepatopancreatic necrosis disease strain (*Vp*AHPND) infection highlighted the scope of developing AMPs as biomarkers (Chiew et al. 2019). Another recent study identified multigene biomarkers for the shrimp white faeces syndrome (WFS). WFS is a wreaking havoc to shrimp industries causing huge loss and there found a connection between the WFS and dysbiosis. Antimicrobial genes ALFs, PENs, and crustin were seen to be upregulated during the course of infection and proposed as potential biomarkers for the disease (Zeng et al. 2020).
- Edible antimicrobial food coatings: Novel idea of using active packaging is gaining interest in recent years. Recently, active shrimp concentrate (SC) from *L. vannamei* acted as antimicrobial agents when used in combination with chitosan–gelatin matrix as edible packaging covers for fish sausages. The authors suggest that the active ingredients inhibited and delayed the growth of fish pathogens and could potentially be due to the presence of antimicrobial peptides, protein-lipid concentrate present in shrimp concentrate (Alemán et al. 2016).

Conclusion

This review aims to provide a comprehensive overview of the shrimp derived peptides and their interdisciplinary applications that could be deployed for the health and betterment of both humans and animals. Marine organisms are rich sources of various AMPs with more excellent activity. The growing threat of antimicrobial resistance (AMR) calls for an immediate alternative for antibiotics. The broad-spectrum activity of the peptide and the delayed resistance makes them eligible candidates in place of antibiotics. The present review envisaged peptides derived from shrimp are the best fit in replace of antibiotics. Exploring the vast opportunity of the global shrimp aquaculture sector for discovering and commercializing AMPs will benefit both the aquaculture and health sectors. Numerous studies have taken place concerning the identification and characterization of AMPs from shrimp, nevertheless less focus has given to the studies related to the mechanism of action of these peptides. There is plenty more to discover and research to mold these peptides into a commercial applicable form.

Acknowledgements The authors are grateful to the Department of Marine Biology, Microbiology & Biochemistry, School of Marine Sciences, Cochin University of Science and Technology.

Author contributions Sheethu Annie Vincent: Conceptualization, writing the original draftPratheesh Mathew: Writing the original draft-Swapna P. Antony: Supervision, Editing the manuscript

Data availability Data sharing is not applicable for this review article as no new data is provided through this article.

Declarations

Conflict of interest The authors declare no competing financial interests or personal relationships that could have appeared to influence the framing of this paper.

Ethical Approval and Consent to Participate This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for Publication Not applicable.

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