Antimicrobial Peptides: Novel Source and Biological Function With a Special Focus on Entomopathogenic Nematode/Bacterium Symbiotic Complex

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The rapid emergence of multidrug resistant microorganisms has become one of the most critical threats to public health. A decrease in the effectiveness of available antibiotics has led to the failure of infection control, resulting in a high risk of death. Among several alternatives, antimicrobial peptides (AMPs) serve as potential alternatives to antibiotics to resolve the emergence and spread of multidrug-resistant pathogens. These small proteins exhibit potent antimicrobial activity and are also an essential component of the immune system. Although several AMPs have been reported and characterized, studies associated with their potential medical applications are limited. This review highlights the novel sources of AMPs with high antimicrobial activities, including the entomopathogenic nematode/bacterium (EPN/EPB) symbiotic complex. Additionally, the AMPs derived from insects, nematodes, and marine organisms and the design of peptidomimetic antimicrobial agents that can complement the defects of therapeutic peptides have been used as a template.

Keywords: antimicrobial peptides, multidrug-resistant pathogens, insects, nematodes, marine

INTRODUCTION

Antimicrobial peptides (AMPs) are small molecules that generally consist of 10–50 amino acids and are highly conserved in a wide range of species, including insects, nematodes, microbes, and mammals. AMPs serve as an essential component of the body’s immune system and defend against exogenous pathogens. They possess significant structural variations in the α-helices, β-strands with one or more disulfide bridges, loop, and extended structures associated with their broad-spectrum activities (Hancock, 2001; Pushpanathan et al., 2013). Other important factors associated with the functional activities of AMPs are size, hydrophobicity, charge, amphipathic stereo-geometry, and...
peptide self-association to the biological membrane (Nissen-Meyer and Nes, 1997; Marcos and Gandía, 2009; Pushpanathan et al., 2013). AMPs can be considered potential drug candidates to treat pathogenic microorganisms due to their broad-spectrum activity, lesser toxicity, decreased resistance development by the target cells, and capability to modulate the host immune response (Hancock and Patrzykat, 2002; Xu et al., 2019). AMPs can ameliorate the drug-resistant crisis and associated toxicity with conventional AMP drugs and also can be employed as an alternative to antibiotics (Lewies et al., 2019). They exhibit several similarities to antibiotics, such as killing microbial cells and targeting a broad spectrum of pathogens, including antibiotic resistance.

Moreover, compared to antibiotics, AMPs have unique epitopes that serve as protease recognition sites, thereby less likely to be targeted by the protease (Zasloff, 2002; Lai and Gallo, 2009). Different mechanisms, such as inhibition of gene expression or protein synthesis, inhibition of cell wall synthesis, or delocalization of bacterial cell surface proteins are commonly employed by the AMPs (Baltzer and Brown, 2011). Most of the AMPs are cationic and capable of adapting to amphipathic conformations. This helps them interact with the negatively charged bacterial cell wall and integrate it into the lipid bilayers (Haney et al., 2017; Zharkova et al., 2019). The success of AMPs against multidrug-resistant pathogens is due to the widescale multitargeted action (Zharkova et al., 2019). They are also active at lower minimum inhibitory concentrations (MICs) as compared to antibiotics. AMPs demonstrate higher killing effects and show a narrower mutation-selection window, accounting for the less likely development of resistance to AMP (Fantner et al., 2010; Yu et al., 2018). They are also active against biofilm-producing antibiotic-resistant microbes and induce non-opsonic phagocytosis. However, the combined use of AMPs with other antimicrobial compounds such as specific antibiotics may play a vital role against multidrug-resistant pathogens and associated adverse health conditions. In addition, some AMPs have been identified to exhibit antiviral activities (Chia et al., 2010; Van Der Does et al., 2010; Chung and Kocks, 2011; Steckbeck et al., 2014; Elnagy and AlKhazindar, 2020). The AMPs play an essential role in modulating immunogenic activities, improving wound healing, enhancing chemokine production, exhibiting anti-inflammatory properties, regulating epithelial cell differentiation, and modulating angiogenesis (Koczulla and Bals, 2007; Mahlapuu et al., 2016; Otvos, 2016; Patruea et al., 2020; Figure 1). Nowadays, scientists are participating in developing enhanced AMPs with novel modes of actions to replace or complement traditional antibiotics to treat various diseases (Morikawa et al., 1992; Wang et al., 2016). So far, 3257 AMPs have been reported from six kingdoms (bacteria, archaea, fungi, protists, plants, and animals) in the Antimicrobial Peptide Database¹ (Wang et al., 2016). This review provides insights into developing different AMPs from novel sources and their multifunctional properties and elaborates their future prospects (Figure 2). Particular focus has been given to the AMPs in bacteria that form a symbiotic relationship with the entomopathogenic nematodes (EPNs), displaying varied modes of actions.

**AMPS IN INSECTS**

Insects represent the largest class in the animal kingdom and are found in most of the biological niches. One of the critical features of their successful adaptation is their resistance to various pathogens. The AMPs play a critical role in innate immunity against insect pathogens (Bulet et al., 1999). They produce a large number of AMPs that varies between species, ranging from 50 (Harmonia axyridis) to 0 (Hermetia illucens) (Gerardo et al., 2010; Vilkinsas, 2013; Vogel et al., 2018). Cecropin, the first insect AMP, was isolated and characterized from Hyalophora cecropia (Steiner et al., 1981). Since then, many insect AMPs have been reported, which are mainly classified into three groups based on the sequence and structural features, i.e., linear peptides with α-helices that lack cysteine residues and cyclic peptides containing cysteine residues and peptides with an overexpression of proline and glycine residues (Hetru, 1998; Bulet et al., 1999). The most explored insect AMPs are defensin, cecropin, drosocin, attacin, diptericin, ponercin, drosomycin, and metchnikowin. However, it is expected that insects may have more AMPs with novel modes of action (Mylonakis et al., 2016).

Cecropins are small peptides that destroy bacterial cell membranes, inhibit proline uptake, and cause leaky membranes (Moore et al., 1996). It has also been reported that cecropin A (CecA) destroys urapathogenic Escherichia coli (UPEC) cells, alone or in combination with nalidixic acid (NAL), and could be a practical approach to treat antibiotic-resistant UPEC infections (Kalsy et al., 2020). CecA from H. cecropia exhibits only antibacterial activity, whereas CecA from Anopheles gambiae exhibits antibacterial and antifungal activities (Bulet et al., 2004). BR003-Ceca from Aedes aegypti actively inhibits multiple species of Gram-negative bacteria (GNB), including A. baumannii (Jayamani et al., 2015). Cec D from Galleria mellonella exhibits vigorous activity against Gram-positive bacterium (GBP) Listeria monocytogenes (Mukherjee et al., 2011). Defensins are the second primary class of inductive insect AMPs active against GBP, including Staphylococcus aureus, but are less active against GNB (Hetru et al., 2003; Gomes and Fernandes, 2010). Few defensins also possess antifungal activities against filamentous fungi, e.g., gallerimycin from the greater wax moth G. mellonella (Langen et al., 2006). Insect defensin-like peptides are found in Leuconotus quinquestratius and Androctonus australis (Cociancich et al., 1993; Ehret-Sabatier et al., 1996). Defensin-like peptide 4 (DLP4) reported from the black soldier fly is active against GBP (Park et al., 2015).

The AMP drosocin, isolated from Drosophila melanogaster, is a 19-residue peptide containing six proline and four arginine residues (McManus et al., 1999). Glycosylated drosocin is active against E. coli and fungi (Imler and Bulet, 2005). These O-glycosylated AMPs are also found in other insects such as Pyrrhocoris apterus (pyrrhocorin), Bombyx mori (lebocins), and Myrmecia gulosa (formations) (Cociancich et al., 1994; Hara and Yamakawa, 1995; Mackintosh et al., 1998; Wu et al., 2018).

¹http://aps.unmc.edu/AP/main.php/
Attacins, glycine-rich AMP, were first discovered in *H. cecropia* and is active against GNB (Hultmark et al., 1983; Carlsson et al., 1991). Attacins from *Spodoptera exigua* exhibit activity against *E. coli*, *Pseudomonas cichorii*, *Bacillus subtilis*, *L. monocytogenes*, *Trypanosoma brucei*, *Citrobacter freundii*, and *Candida albicans* (Hu and Aksoy, 2005; Kwon et al., 2008; Bang et al., 2012). Attacins and attacin-related proteins are also isolated from *B. mori*, *Heliothis virescens*, *Trichoplusia ni*, *Samia cynthia ricini*, and *Musca domestica* (Dushay et al., 2000; Geng et al., 2004).

Diptericin (9 kDa), found in *D. melanogaster*, *Sarcophaga peregrina*, and *Mayetiola destructor*, is active against GNB such as *E. coli*, *Erwinia herbicola* T, and *E. carotovora* (Keppi et al., 1989; Ishikawa et al., 1992; Reichhart et al., 1992).

However, limited reports are available on antifungal peptides in insects such as drosomycin from *D. melanogaster*, termicin from termites, helimycin from *H. virescens*, and gallerimycin peptide from *G. mellonella* (Fehlbaum et al., 1994; Da Silva et al., 2003; Schuhmann et al., 2003). The antifungal peptide drosomycin is active against fungal pathogens, whereas thanatin is effective against a broad range of β-lactamase-producing *E. coli* (Bulet et al., 1999; Hou et al., 2011).

Xu et al. (2019) reported a novel Moricin (Px-Mor) from the diamondback moth that showed a broad-spectrum activity against GPB, GNB, and fungi, including the opportunistic human pathogen *Aureobasidium pullulans*. They suggested that Px-Mor can be used as a potential topical antimicrobial agent (Xu et al., 2019). These results indicate the importance of insect-derived AMPs against pathogens and could be further employed against multidrug-resistant pathogens or in combination with existing antibiotics (Table 1).

**AMPS IN NEMATODE**

Antimicrobial peptides are produced by microorganisms associated with insect symbioses and play a significant role in maintaining the symbiotic microbe in specific anatomical
### TABLE 1 | Recently identified insect AMPs with their mechanism of action.

| Name of AMP | Type of AMP | Source | 3D structure | Pathogenic species | Molecular mechanism | Inhibitory concentration | References |
|-------------|-------------|--------|--------------|--------------------|---------------------|-------------------------|------------|
| ETD151 (Helomicin) | Defensin | Heliothis virescens | Combine helix and beta structure | Botrytis cinerea | Interact with glucosylceramides of the fungal membrane | $IC_{50} = 0.59 \mu M$ | Aumer et al., 2020 |
| Holosins | Ixodes holocyclus | Cys-stabilized $\alpha/\beta$-fold | Staphylococcus aureus, Listeria grayi, F. graminearum, and C. albicans | Peptide–lipid interactions result in the formation of membrane penetrating pores | MIC = 8 $\mu M$ | Cabanas-Cruz et al., 2019 |
| Oxysterins | Cecropin | Oxytornon conspicillatum | Linear $\alpha$-helix | Staphylococcus saprophyticus, Klebsiella pneumoniae, and Pseudomonas aeruginosa | Membrane lysis due to formation of pores | MIC = 12.5 $\mu g/ml$ | Toro Segovia et al., 2017 |
| Cecropin D | Galleria mellonella | $\alpha$-Helix | K. pneumoniae (MDR), P. aeruginosa (MDR) | Membrane lysis due to formation of pores | MIC = 256 $\mu g/ml$ | Ocampo-Ibáñez et al., 2020 |
| Cecropin B | Antheraea pernyi | P. aeruginosa | | Membrane lysis due to formation of pores | MIC = 0.2 $\mu g/ml$ | Wu et al., 2012; Yang et al., 2018; Gholizadeh and Moradi, 2020 |
| Cecropin AD | Hyalophora cecropia | Staphylococcus aureus | | Membrane lysis due to formation of pores | NS | Shin and Park, 2019 |
| Hi-attacin | Attacin | Hermetia illucens | Unknown | E. coli and methicillin-resistant Staphylococcus aureus | Blocking the synthesis of the major outer membrane proteins, thus disturbing the integrity of the cell wall | NS | Ursic-Bedoya et al., 2011 |
| Prolixin | Rhodnius prolixus | E. coli, Citrobacter freundii, Enterobacter aerogenes, and Bacillus coagulans | | | MIC = 1.6 $\mu M$ | Yang et al., 2018; Yang et al., 2020 |
| StLeb-1 | Lebocin | Spodoptera littura | Rich | E. coli and B. subtilis | Disrupt cell membrane and cause cell elongation | MIC = 50 $\mu M$ | Berthold and Hoffmann, 2014; Feng et al., 2020 |
| Apidaecin IB | Drosocin | Apis cerana | Rich | Escherichia coli and Klebsiella pneumoniae | Binds to the substrate binding site of E. coli DnaK to compete with natural substrates | NS | Ursic-Bedoya et al., 2011 |
| Api795 | Apidaecin | P. aeruginosa | | Insert into bacterial mimic membranes and initiates a structural change leading to a thicker and more rigid membrane layer | MIC = 8 $\mu g/ml$ | Bluhm et al., 2016 |
| EtDip | Diptericin | Eristalis tenax | Unknown | Candida albicans FH2173 and Mycobacterium smegmatis ATCC 607 | Interacts with the fungal enzyme $(1,3)$-glucanoyltransferase Gel1 (FgBGT), which is one of the enzymes responsible for fungal cell wall synthesis | MIC > 1024 $\mu g/ml$ | Hirsch et al., 2020 |
| Mtk | Metchnikowin | Drosophila melanogaster | Rich | Fusarium graminearum | Interacts with the fungal enzyme $(1,3)$-glucanoyltransferase Gel1 (FgBGT), which is one of the enzymes responsible for fungal cell wall synthesis | MIC = 64 $\mu g/ml$ | Moghaddam et al., 2017 |

(Continued)
### Table 1 (Continued)

| Name of AMP | Type of AMP Source | Source | Molecular mechanism | Pathogenic species | 3D structure | Inhibitory concentration | Pathogenic species | References |
|-------------|-------------------|--------|---------------------|-------------------|--------------|--------------------------|-------------------|------------|
| Ponericin-Q42 | Pore-forming toxins | Apis mellifera | 
| \( \alpha \)-Helical folds | E. coli, E. coli K12, and P. aeruginosa | 
| Membrane blebbing, formation of swollen cells and finally membrane death | \( \alpha \)-Helical | 
| Increase the production of cellular ROS and bind with genome DNA | \( \alpha \)-Helical | 
| Inhibit the protein folding activity of the ATP-dependent DnaK/DnaJ molecular chaperone system | \( \alpha \)-Helical | 
| Interact with bacterial membrane | \( \alpha \)-Helical | 
| MIC = 0.2 \( \mu \)M | \( \alpha \)-Helical | 
| MIC = 0.6 \( \mu \)M | \( \alpha \)-Helical | 
| MIC = 10 \( \mu \)M | \( \alpha \)-Helical | 
| MIC and MFC = 30 \( \mu \)g/ml | \( \alpha \)-Helical | 
| MIC = 61 \( \mu \)g/ml | \( \alpha \)-Helical | 
| MIC = 427 \( \mu \)M | \( \alpha \)-Helical | 
| MIC = 4 \( \mu \)g/ml | \( \alpha \)-Helical | 
| MIC = 40 \( \mu \)g/ml | \( \alpha \)-Helical | 

Another group of AMPs called the caenopores belong to the saposin-like protein (SAPLIP) superfamily detected in *Caenorhabditis elegans*. It contains conserved positions of six cysteine residues. Caenopore-1 (SPP-1), caenopore-5 (SPP-5), and caenopore-12 (SPP-12) exhibit antimicrobial activity against *B. megaterium*, *E. coli*, and SPP-12 *Bacillus thuringiensis* (Roeder et al., 2010; Hoeckendorf et al., 2012).

Defensins are the most studied AMPs in nematodes. *Ascaris suum* antibacterial factors (ASABFs) was the first nematode defensin identified in *C. elegans*. They are short AMPs with eight cysteine residues that form four disulfide bonds except for ASABF-6Cys-\( \alpha \) (Minaba et al., 2009; Tarr, 2012). These peptides are primarily active against GPB, especially the common pathogen *S. aureus*. However, it is less effective against GNB and yeast (Tarr, 2012). A recent study by Lim et al. (2016) reported two novel *C. elegans* AMPs (NLP-31 and Y43C5A.3) that exhibit antimicrobial activity against *Burkholderia pseudomallei*, the causative agent of melioidosis, by interfering with DNA synthesis. They also revealed that these AMPs might act by modulating host cytokine production to interfere with the inflammatory response, and modifications could enhance anti-*B. pseudomallei* activities (Lim et al., 2016).
AMPS LINKED WITH EPN/EPB SYMBIOTIC COMPLEX

Several bacterial genera belonging to the Enterobacteriaceae family are mutually associated with the EPNs (Boemare, 2002). These EPNs, with their symbiotic bacteria, are lethal to many soil insects, as they synthesize diverse secondary metabolites, including small AMPS. These nematode-associated microbes exist in two distinct phases: phase 1, where they are generally associated with the nematodes, and phase 2, where they may also colonize with the nematode. However, they have never been reported to be associated with the naturally occurring nematodes. Both phases have distinguished physiological, biochemical, and behavioral features; also phase 1 is considered more virulent than phase 2 (Akhurst et al., 1990; Volgyi et al., 1998; Abdel-Razek, 2002; Sugar et al., 2012). During the infective juvenile (IJ) stage, the nematodes enter inside the insects by piercing the body wall or via natural openings and releasing these bacteria inside the hemocoel. They reproduce exponentially, producing bioactive compounds with broad-spectrum antimicrobial activities (Sanda et al., 2018). They provide nutrients to the nematodes and protect them from environmental predators such as bacteria and fungi. They also compete for nutrition with other microbes, including the saprophytic soil microbes and the bacteria present in the insect gut or cuticle of the nematode. The elimination of the competitors is facilitated by the production of colicin E3-type killer proteins, insect toxin complexes, phage-derived bacteriocins, and several secondary metabolites (Thaler et al., 1995; Ffrench-Constant and Waterfield, 2006; Singh and Banerjee, 2008; Bode, 2009; Piel, 2009). The presence of high content of non-ribosomal peptide synthetase (NRPS) and polyketide synthase (PKS) genes facilitates them to produce novel and new bioactive molecules (Tobias et al., 2017). These bioactive molecules disrupt the insect's metabolic and functional properties, leading to septicemia (Khandelwal and Banerjee-Bhatnagar, 2003; Tran and Goodrich-Blair, 2009; Ellis and Kuehn, 2010; Brivio et al., 2018). Nematodes also play a significant role in the pathogenicity of the nematode-bacterial complex (Han and Ehlers, 1999; Ellis and Kuehn, 2010; Brivio et al., 2018). The EPNs, along with the mutualistic bacteria, kill their host within 48–72 h (Forst and Nealson, 1996). These features are now being exploited for the biological control of pests (Brivio and Mastore, 2018).

The bacterial genus Xenorhabdus is often found in close association with EPNs of the family Steinernematidae (Webster et al., 2002). Xenorhabdus synthesizes and releases antibiotic compounds in the host hemocoel that suppresses the microbial competitors, thereby manipulating the environment to promote growth, proliferation, and nematode development (Vallet-Gely et al., 2008; Richards and Goodrich-Blair, 2009; Gaugler, 2018). The antimicrobial compounds produced by these bacterial genera are highly toxic to the insect but not toxic to the nematodes. Various surface structures such as pili/fimbriae, flagella, and the outer membrane vesicles (OMVs) present in the Xenorhabdus interact with the host and promote adhesion and invasion of the host tissues. They also promote larvicidal activity by releasing proteases, lytic factors, and phospholipase C (Brivio et al., 2018).

Ribosomal-encoded bacteriocins (xenohabdicins) are found in Xenorhabdus nematophilus. These AMPs compete against more closely related bacteria, such as other Xenorhabdus and Photorhabdus strains (Thaler et al., 1995). The indole-containing Xenematide from Xenorhabdus nematophilus exhibits moderate antibacterial and insecticidal activities (Lang et al., 2008). Two novel depsipeptides, xenematides F and G, were isolated from Xenorhabdus budapestensis SN84 with high antibacterial activity (Xi et al., 2019).

The cyclic peptide-antimicrobial-Xenorhabdus (PAX) lipopeptides, obtained by the fermentation of the X. nematophilum F1 strain, exhibit significant activity against plants and human fungal pathogens and moderately effective against a few bacteria and yeast (Gualtieri et al., 2009). Two novel AMPs GP-19 and EP-20 from the bacterial strain X. budapestensis NMC-10. GP-19 exhibited inhibitory activity mainly against bacteria, while EP-20 was highly effective against plant pathogens. The synthetic GP-19 and EP-20 peptide exhibited inhibitory activities against the fungal pathogen Verticillium dahlia and Phytophthora capsici with EC$_{50}$ values of 17.54 and 3.14 µg/ml, respectively (Xiao et al., 2012).

The AMPs xenocoumacin 1 (XCN 1) and 2 (XCN 2), from the bacterium X. nematophilus, is effective against GPB and fungi. This peptide is synthesized by the PKS/NRPS multienzyme (xcnAN) (McNerney et al., 1991; Reimer, 2013). Six novel linear peptides (rhodopeptides) in X. nematophilus and two other rhodopeptide derivatives by X. cabanillasii were also identified (Reimer et al., 2013).

Nematophins, from X. nematophilum YL001, inhibit mycelial growth of Rhzoctonia solani and Phytophthora infestans with an EC$_{50}$ value of 40.00 and 51.25 µg/ml, respectively, and can be employed as a potential biopesticide in the agriculture sector (Zhang et al., 2019). Similarly, the novel peptide, xenoamicin, tridecadepsipeptides with hydrophobic amino acids, from the entomopathogenic X. doucetiae DSM 17909 and X. mauleonii DSM 17908 was effective against Plasmodium falciparum (Zhou et al., 2013).

Another dipeptide xenobactin was isolated from Xenorhabdus sp., strain PB30.3, and szentiamide from X. szentirmai. Both AMPs are active against P. falciparum and have moderately effective against T. brucei rhodesiense and Trypanosoma cruzi (Nollmann et al., 2012; Grundmann et al., 2013). Similarly, the depsipentapeptide chaiyaphumine A from Xenorhabdus sp. PB61.4 was effective against P. falciparum (IC$_{50}$ of 0.61 µM) and other protozoal tropical disease-causing agents (Grundmann et al., 2014). Xenorhabdus indica can produce depsipeptides and lipodepsipeptides with an additional fatty acid chain linked to one of the amino acids, also called taxillalids (A–G), and exhibits antiprotzoal activity (Kronenwerth et al., 2014). Taken together, these reports suggest that the mutualistic association between Xenorhabdus and Steinernematidae could serve as a potential source for novel AMPs against bacteria, fungi, and protozoal disease-causing agents.

The bacterium Photorhabdus spp. forms a symbiotic relationship with the EPNs of the genus Heterorhabditis (Gerrard et al., 2006). They cause pathogenicity in most insects post invading the hemolymph (Boemare et al., 1997). Genomic
The AMPs from Photorhabdus spp. and photoditritide (B. thuringiensis) and a developmentally regulated protein from a beetle (Leptinotarsa decemlineata) (Duchaud et al., 2003; Waterfield et al., 2005). Research on the larvicidal activity of Photorhabdus spp. showed that Photorhabdus insect-related (Pir) protein is associated with high toxicity against the primary vector of dengue virus A. aegypti and Aedes albopictus (Ahantrag et al., 2009). These novel insecticidal proteins could further be exploited to develop alternative agents to control insect pests.

Genomic analysis of Photorhabdus subsp. laumondii strain TT01 indicates the presence of several enzymes associated with the secondary metabolite biosynthesis. The genomic sequence analysis identifies biosynthetic gene clusters associated with the synthesis of linear or cyclized peptides, lipopeptides, or depsipeptides; NRPS; unusual fatty acid synthase or a FAS/PKS hybrid; and siderophore biosynthesis (Bode, 2009). Photorhabdus spp. also produces numerous antimicrobials such as isopropyl stilbene, ethylstilbenes, anthraquinones (AQs) photobactin, ethyl stilbene, epoxystilbene, and ulbactin E (Li et al., 1997; Webster et al., 2002; Bode, 2009). The bioactive compounds exhibit a broad range of antimicrobial activities. Photorhabdus antibacterial compounds include trans-stilbenes and anthraquinone pigments (Boemare and Akhurst, 2002) that have enthralled substantial interest in the agronomic and pharmaceutical sectors (Webster et al., 2002; Hazir et al., 2016). Phthalic acid or 1,2-benzene dicarboxylic acid purified from Photorhabdus temperata M1021 exhibits an antibacterial activity with MIC values of 0.1 and 0.5 M (Ullah et al., 2014), benzaldehyde exhibits an antibacterial activity with MIC values of 6 and 10 mM, and antifungal activity with MIC values between 8 and 10 mM (Ullah et al., 2015). P. temperata subsp. temperata inhibits the growth of 10 strains of drug-resistant bacteria including carbapenem-resistant Enterobacteriaceae, which strain especially shows resistance toward many classes of available antibiotics and causes severe infections with a 50% mortality rate (van Duin et al., 2013).

**The Targets and Mechanism of Action of AMPs Derived from Nematobacterial Complexes**

The AMPs from Xenorhabdus spp. and Photorhabdus spp. are non-lethal to nematode but toxic to insect pathogens and other opportunistic microorganisms with unique targets and modes of action. This section highlights some of the recently identified AMPs from EPB with novel modes of action, namely, nematophin, odiolohadin, darobactin, and photoditritide (Figure 3).

**Nematophin**

First isolated from X. nematophilus strain BC1 (Li et al., 1997), it contains 3-indoleethyl (3'-methyl-2'-oxo) pentanamide with an N-terminal α-keto group and a C-terminal tryptamine residue. Recently, few novel nematophin analogs were identified from Xenorhabdus strains (Cai et al., 2017). Nematophin is effective against S. aureus (MIC = 0.125 µg/ml) (Li et al., 1997), methicillin-resistant S. aureus (MRSA) (MIC = 1.5 µg/ml), and fungal pathogens, Botrytis cinerea (MIC = 12 µg/ml) (Li et al., 1997) and R. solani (MIC = 40 µg/ml) (Zhang et al., 2019). The synthetic nematophin analog with N-methyl substitution exhibits nanomolar activity toward S. aureus (15 ng/ml), S. intermedii 9503 (50 ng/ml) (Himmler et al., 1998), S. hyicus (60 ng/ml), MRSA ATCC 43300 (31 ng/ml), and methicillin-susceptible S. aureus ATCC 29213 (125 ng/ml) (Wescue et al., 2019). Recent studies indicate that nematophin is a potent biopesticide against a necrotrophic fungal pathogen R. solani. It interferes with the sclerotial development and hyphal morphology of R. solani at 40.00 µg/ml and germination at 15.00 µg/ml. The ultrastructure shows that the hyphae becomes twisted, shriveled, and deformed at the growing points after the exposure to nematophin at 40.00 µg/ml, and the mitochondrial structural abnormalities such as reduction in number, vacuolar degeneration, and fuzzy cristae are also observed (Figure 3A).

**Odiolohadin**

This is a new class of AMP with broad-spectrum activity encoded by the enzymes (of NRPS gene cluster) of X. nematophila. This peptide binds to the decoding center of the small ribosomal subunit, leading to faulty coding procedure and prohibits non-cognate aminoacyl-tRNAs binding (Pantel et al., 2018). Odiolohadin can directly bind with the new site on 16S rRNA (Figure 3B) and with the anticodon loop of the A-site aminoacyl-tRNA concurrently, resulting in the precision of translation decreased. At very high concentrations, odilorhabin inhibits the ribosome movement on mRNA (Pantel et al., 2018). Studies reported that odilorhadin acts against Gram-negative and Gram-positive bacterial pathogens, including carbapenem-resistant Enterobacteriaceae, which strain especially shows resistance toward many classes of available antibiotics and causes severe infections with a 50% mortality rate (van Duin et al., 2013).

**Darobactin**

It is a novel peptide antibiotic produced by Photorhabdus khanii HGB1456 (Imai et al., 2019) that is effective against several Gram-negative drug-resistant pathogens. Instead of targeting the enzymes, darobactin targets outer membrane chaperone BamA (Figure 3C), catalyzing the insertion and folding of B-barrel outer membrane proteins in many Gram-negative pathogens. As the target of darobactin is a cell surface protein, there is no permeability obstacle encountered (Imai et al., 2019). No antibiotics were reported to act on the two surface proteins, namely, BamA and LptD, present on the GNB; therefore, darobactin could act as a potential drug candidate due to its
TABLE 2 | Antimicrobial peptides from nematobacterial complexes with their inhibitory concentrations.

| Name of AMP | Source | Pathogenic species | Inhibitory concentration | References |
|-------------|--------|--------------------|--------------------------|------------|
| Xenematide C | Xenorhabdus budapestensis SN19 | Botrytis cinerea | EC$_{50}$ = 22.71 µg/ml | Xing-zhong et al., 2016 |
| Xenematides F | Xenorhabdus budapestensis SN84 | P. aeruginosa | MIC = 32 µg/ml | Xi et al., 2019 |
| Xenemates G | B. subtilis | MIC = 16 µg/ml | | |
| PAX lipopeptides | X. koiSanae SB10 | B. subtilis subsp. subtilis Escherichia coli Candida albicans | NS | Dreyer et al., 2019 |
| Xenocoumacin 2 | EPN Rhabditis sp. | Penicillium expansum | MIC = 2 µg/ml | Kumar et al., 2013 |
| Nematophin | Xenorhabdus nematophilia YL001 | Rhizoctonia solani Phytophthora infestans | EC$_{50}$ = 40.00 µg/ml | Zhang et al., 2019 |
| Nematophin | Xenorhabdus budapestensis PB62.4 | Staphylococcus aureus | EC$_{50}$ = 61.25 µg/ml | Cai et al., 2017 |
| GP-19 EP-20 | Xenorhabdus budapestensis NMC-10 | Verticillium dahlia Phytophthora capsici | EC$_{50}$ = 3.14 µg/ml | Xiao et al., 2012 |
| Threonine–glutamine dipeptide domain containing protein | Bacillus cereus | E. coli, S. aureus, and B. subtilis | MIC = 62.56 µg/ml | Anju et al., 2015 |
| Xenocoumacin 1 | Xenorhabdus nematophilia | Botrytis cinerea | Inhibition rate of 100 ml/L cell-free filtrate on the mycelial growth of the pathogens is 100% | Guo et al., 2017 |
| Xenocoumacin 2 | Xenorhabdus assam-isolate (SG as1) | Macrophomina phaseolina | EC$_{50}$ = 55.98 µg/ml | Sharma et al., 2016 |
| Cabanillasin | Xenorhabdus cabanillasii | Fusarium oxysporum | IC$_{50}$ = 6.25 µg/ml | Houard et al., 2013 |
| Xenobactin | Xenorhabdus sp. PB30.3 | Micrococcus luteus Plasmodium falciparum NF 54 Trypanosoma brucei rhodesiensis STIB900 Trypanosoma cruzi Tulahuen C4 | IC$_{50}$ = 64 µg/ml | Grundmann et al., 2013 |
| Xenortide D | Xenorhabdus nematophilia | Plasmodium falciparum Trypanosoma brucei | IC$_{50}$ = 12.45 µg/ml | Grundmann et al., 2013 |
| Taxiloids | Xenorhabdus indica (DSM 17382) | Plasmodium falciparum | NS | Reimer et al., 2014 |
| Phototemtide A | Photobacteroides temperata Meg1 | Plasmodium falciparum Trypanosoma brucei rhodesiense | IC$_{50}$ = 9.8 µM | Zhao L. et al., 2020 |

distinctive sizeable molecular structure fused rings and unusual cell surface target (Konovalova et al., 2017).

Photoditritide

Photoditritide is the first non-proteinogenic peptide reported from P. temperata Meg1 through promoter exchange (Maglangit et al., 2021). Photoditritide 19 consists of two tyrosines, two homo-arginines, and two tryptophans (Bode et al., 2015). It is effective against E. coli (MIC = 24 µM), M. luteus (MIC = 3.0 µM), and antiprotozoal activity against P. falciparum (IC$_{50}$ = 27 µM), T. cruzi (IC$_{50}$ = 71 µM), and T. brucei rhodesiens (IC$_{50}$ = 13 µM) (Bode et al., 2015).

The increasing evidence of antibiotic resistance is a serious issue. Drug-resistant pathogens develop new resistance mechanisms and interfere in the treatment of common infections. Moreover, multidrug resistance pathogenic strains have developed tolerance against most of the available antibiotics. Researchers searching for novel sources of antimicrobial agents through synthetic compound library screening have mostly failed to get efficient antimicrobial agents (Payne et al., 2007).

Therefore, exploiting new natural antimicrobial sources to fill the research gap in antimicrobial drug discovery is a promising approach. Most of the antibiotics used to date belong to soil actinomycetes. The present review aims to compile novel natural sources, highlighting the unnoticed and ignored sources to identify new AMPs with a unique mode of action. The marine ecosystem presents a vast repository of microorganisms, invertebrates, and vertebrates that produce various natural products and AMPs with the perspective of treating several infectious diseases (Bertrand and Munoz-Garay, 2019).

MARINE-DERIVED ANTIMICROBIAL PEPTIDES

The marine ecosystem encompasses an unprecedented variety of organisms that have shown remarkable contribution in discovering and developing novel biomolecules, nutraceuticals, and secondary metabolites that pave the way to produce antimicrobial agents (Malve, 2016; Sekurova et al., 2019; Figure 1). AMPs derived from marine sources
are novel and revolutionary therapeutic agents with distinctive pharmacological properties such as antimicrobial, antiproliferative, antioxidant, anticoagulant, antihypertensive, antidiabetic, and antiobesity properties (Jo et al., 2017).

**Antimicrobial Peptides Derived From Marine Invertebrates**

Marine invertebrates produce AMPs to activate innate immune machinery to recognize, neutralize, and eliminate invading pathogens (Loker et al., 2004). A wide variety of corals produce structurally unique bioactive metabolites that can serve as significant novel compounds in drug development against various human diseases. For example, the marine fungus *Simplicillium* sp. associated with soft coral *Sinularia* sp. synthesizes five new peptides, including *Sinularia* peptides A–E. These bioactive AMPs exhibit significant antimicrobial activity against *Mycobacterium tuberculosis*, *Colletotrichum asianum*, and *Pyricularia oryzae* Cav. Mollusks such as *Mytilus edulis*, *Ruditapes decussatus*, and oyster *Mytilus galloprovincialis* produce AMPs such as myticins and mytilin. A cyclic hexapeptide, cyclo-(Gly-Leu-Val-Ile-Ala-Phe), bacicyclin isolated from *Bacillus* sp. associated with *M. edulis*, exhibits antibacterial activities against clinically relevant bacterial strains such as *S. aureus* and *Enterococcus faecalis* (Wiese et al., 2018; Zanjani et al., 2018). AMPs derived from marine invertebrates can modulate the lifecycle of bacterial biofilm and also inhibit biofilm formation. Crustin, an antibacterial protein, consists of alanine or threonine, glycine, and glutamine residues at their cleavage site and is derived from the hemolymph of crustaceans (Destoumieux-Garzón et al., 2016). It effectively inhibits biofilm formation of various antibiotic-resistant bacterial strains, including *B. pumilis* and *B. thuringiensis* and also is effective against *Aeromonas hydrophila* and *E. coli* (Rekha et al., 2018; Sivakamavalli et al., 2020). A novel antibacterial peptide named PcnAMP, extracted from *Procambarus clarkia* (Pcn) (a red swamp crayfish), exhibits a significant inhibitory effect against Gram-positive and GNB strains such as *S. aureus* and *M. luteus* (Zhao B. R. et al., 2020). AMPs from ascidian *Didemnum* sp. exhibit an antibacterial effect against human pathogens *E. faecalis*, *S. marcescens*, *S. typhimurium*, and *S. aureus* at MICs of 2.30, 2.17, 2.05, and 1.95 µg/ml, respectively (Arumugam et al., 2020). The AMPs halocyntin and papillosin from tunicate *H. papillosa* exhibit antibacterial activity against *M. luteus* and *E. coli* (Palanisamy et al., 2017). A novel AMP myticusin-beta isolated from the mantle of *Mytilus coruscus* exhibits a broad range of antibacterial activity and acts as a substitute to antibiotics (Oh et al., 2020). Therefore, the diverse forms of marine invertebrates act as natural reservoirs for novel AMPs, which can be exploited for the treatment of various microbial infections (Thoms et al., 2007; Destoumieux-Garzón et al., 2016; Table 3).

**Antimicrobial Peptides From Marine Microorganisms**

Marine microbial systems are the significant resources of AMPs with unique pharmacological features, including antimicrobial, cytostatic, animal growth, immunosuppressant, antiviral, antimalarial, antiparasitic, promoters, and insecticides activities (Semreen et al., 2018). AMPs extracted from symbiotic marine microorganisms exhibit enhanced broad-spectrum antimicrobial activity. These natural compounds are now being exploited to resolve the microbial drug-resistance problem. Hyporporatinal A, an anti-*Candida* peptaibol, a moronecidin-like peptide from *Trichoderma orientale* strains, symbiotic fungi of Mediterranean marine sponge *Cymbaxinella damicornis*, inhibits the growth of clinical isolates of *C. albicans*, Gram-positive and Gram-negative bacteria (Touati et al., 2018). Cyclic lipopeptide Fengycins from marine bacterium...
An antimicrobial peptide from marine invertebrates

| Peptide | Source of peptide | Mode of action | Inhibitory concentration | References |
|---------|------------------|----------------|--------------------------|------------|
| Sinulariapptides A–E | Coral Sinularia sp. | Inhibitory effects against protein tyrosine phosphatases of Mycobacterium tuberculosis (MptpA and MptpB) | IC50 values of 35.0 and 25.9 µM against MptpA and MptpB | Dai et al., 2018 |
| Bacicyclin | Mytilus edulis | Cell membrane damage of Enterococcus faecalis and Staphylococcus aureus | MIC values of Enterococcus faecalis and Staphylococcus aureus was noted to be 8 and 12 mM, respectively | Wiese et al., 2018 |
| Crustin | Portunus pelagicus | The growth reduction and biofilm inhibition potential of on Gram-positive bacteria and Gram-negative bacteria | MIC of both Gram-positive and Gram-negative bacteria was noted to be 30 and 20 µg/ml, respectively | Rekha et al., 2018 |

An antimicrobial peptide from marine microorganisms

| Peptide | Source of peptide | Mode of action | Inhibitory concentration | References |
|---------|------------------|----------------|--------------------------|------------|
| Hyporientalin A | Trichoderma orientale | Growth inhibitory effects toward clinical isolates like Candida albicans | MICs of Candida albicans species (247FN and 098 VC) was noted to be 2.55–4.92 µM, respectively | Touati et al., 2018 |
| Fengycins | Bacillus subtilis | Inducing the mitochondrial membrane potential (MMP), reactive oxygen species (ROS), downregulate the ROS-scavenging enzymes and chromatin condensation in plant-pathogenic fungus Magnaporthe grisea | | |
| EeCentrocin 1 | Echinus esculentus | Cell membrane damage | MIC of Corynebacterium glutamicum and S. aureus (MIC = 0.78 µM) | Solstad et al., 2019 |
| Tetrapeptides 1 | Streptomyces sp. | Growth inhibition of Burkholderia gladioli and Burkholderia glumae | MIC was noted to be 0.068 and 1.1 mM in Burkholderia gladioli and Burkholderia glumae | Betancur et al., 2019 |
| Thr-Pro-Asp-Ser-Glu-Ala-Leu (TPDSEAL) | Porphyra yezoensis | The surface of S. aureus became blurred, loose, irregular, and cell wall damage | | Jiao et al., 2019 |

An antimicrobial peptide from marine vertebrates

| Peptide | Source of peptide | Mode of action | Inhibitory concentration | References |
|---------|------------------|----------------|--------------------------|------------|
| Epinecidin-1 | Epinephelus coioides | Disrupted the membrane of metronidazole-resistant Trichomonas vaginalis | Minimal Epi-1 concentration was noted to be 62.5 µg/ml to produce 100% growth inhibition of Trichomonas vaginalis | Huang et al., 2019 |
| Tissue factor pathway inhibitor 1 (TFPI-2) | Sciacnop ocellatus | TFPI-2 destroying cell membrane integrity, penetrating the cytoplasm and inducing degradation of genomic DNA and total RNA | MICs of TFPI-2 against M. luteus, S. aureus, V. litoralis, V. ichthyicenteri, V. vulnificus, and V. ochrohalim were 3, 6, 11, 85, 170, and 340 µM, respectively | He et al., 2018 |
| Caspian trout (ChHep) | Salmo caspius | The growth inhibition of infectious bacteria | MICs concentration was noted to be 50 and 12.5 µM for Aeromonas hydrophila and Bacillus subtilis | Shirdel et al., 2019 |

B. subtilis (BS155) is effective against the plant-pathogenic fungus Magnaporthe grisea. Host-dependent marine microbes are excellent sources of many active antimicrobial cyclic peptides (e.g., the cyclopipopeptides cyclodysidins A–D). These peptides, secondary metabolites of Streptomyces sp. associated with sponge Dysidea tupha, exhibit broad-spectrum antimicrobial activities (Indraningrat et al., 2016). Different marine gamma-proteobacteria associated with seaweeds, particularly, Pseudomas sp., are the primary sources in cyclotetrapetide cyclo-isoleucyl-prolyl-leucyl-alanyl), cyclic heptapeptide, scopularides A and B, and ogipeptin A–C. These peptides exhibit intense antimicrobial and anthelmintic activities. Ogipeptin is a powerful agent suppressing the immunostimulatory role of lipopolysaccharides present in the cell wall of GNB (Betancur et al., 2019). Similarly, the marine sponge Tethya aurantium associated with fungus Scopulariosis brevicaulis synthesizes cyclodepsipeptides scopularides A and B that exhibit effective cytotoxic activity against pathogens (Agrawal et al., 2017). New cyclic lipopeptides maribasins A and B from the broth culture of marine microorganism B. marinus exhibit broad-spectrum activities against phytopathogens such as Fusarium oxysporum, Fusarium graminearum, Verticillium alboatrum, Alternaria solani, and R. solani with the MICs of 25–200 mg/ml (Zhang et al., 2010). Additionally, the two new cyclic tetrapeptides, from the marine strain Streptomyces sp., are effective against Burkholderia gladioli and Burkholderia glumae at MIC of 0.068 and 1.1 mM, respectively. Furthermore, tetrapeptide-2 is effective against B. glumae (MIC = 1.1 mM) and fungal phytopathogens (Betancur et al., 2019). Hence, the diversified marine microorganisms prove to be an effective substitute to the existing antibiotics, thereby reducing the probability of antibiotic-resistant pathogens (Table 3).
Antimicrobial Peptides From Marine Vertebrates

Antimicrobial peptides in marine vertebrates are mainly localized in body fluids, mucous layers, and epithelial surfaces (Edilia Avila, 2017). AMPs participate in body defense mechanisms to eliminate the invading pathogens and enhance physiological and metabolic processes such as toxin neutralization, wound healing, angiogenesis, and iron metabolism. For instance, epinecidin-1 (Epi-1) disrupts the cell membrane of metronidazole-resistant *Trichomonas vaginalis* and terminates the pathogen with a minimal dose of 62.5 µg/ml. *T. vaginalis* treated with different concentrations of Epi-1 (62.5, 125, 250, or 500 µg/ml) exhibits 100% growth inhibition (Huang et al., 2019). 3C-terminal peptide tissue factor pathway inhibitor 1 (TFPI-1) from *Cyprinus carpio* (common carp) exhibits bactericidal effects against *M. luteus*, *S. aureus*, and *Vibrio vulnificus* (Su et al., 2020). Orange-spotted grouper (*Epinephelus coioides*) derived from AMP EPI is effective against GPB (Su and Chen, 2020). Cysteine-rich Hepcids (CtHep) from vertebrates such as fish, reptiles, and amphibians can significantly inhibit *Streptococcus iniae* and *A. hydrophila* (Shirdel et al., 2019). Marine betta fish *Betta splendens* produce four families of AMPs, including defensins, piscidins, hepcidins, and LEAP-2, which vigorously suppress the growth of fungi, bacteria, virus, and parasites (Amparyup et al., 2020). A short novel peptide synthesized from the core region of the LCNKL2 of a marine fish *Larimichthys crocea* inhibits *S. aureus* and *Vibrio harveyi* (Zhou et al., 2019). Antibacterial activity of piscidin-5 like AMP has been reported from *L. crocea* (Pan et al., 2019). Therefore, AMPs are essential to induce adaptive response and participate in a vertebrate’s metabolic and reproductive processes (Table 3).

CONCLUSION

The exponentially increasing cases of antibiotic resistance requires the introduction of novel and alternative drug molecules. Insects, nematodes, insect–nematode–bacterial associations and marine organisms could be promising sources for natural AMPs to address the challenges of multidrug-resistant infections. The conventional method of overmining natural antibiotic sources has failed to develop new drugs to overcome drug resistance. Genomic analysis indicates the presence of several gene clusters for the novel secondary metabolite biosynthesis. The exploitation of these secondary metabolites might lead to the discovery of potential antimicrobial compounds. This review thereby highlights the symbiotic bacteria–EPN complexes as prospective antimicrobial peptide sources and opens the window to new sources of intervention and invention of natural bioactive compounds to combat antimicrobial resistance. Further research is required to understand the metabolic pathways to optimize the conditions for large-scale production and commercialization of these drug molecules as adequate substitutes.

AUTHOR CONTRIBUTIONS

SD, FJ, and XX conceptualized the manuscript. SD, AP, and CM drafted the manuscript. AP was responsible for preparing the figures in the manuscript. FJ, NS, SD, AP, and CM assisted in revising the manuscript. All authors contributed to the article and approved the submitted version.

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AUTHOR CONTRIBUTIONS

SD, FJ, and XX conceptualized the manuscript. SD, AP, and CM drafted the manuscript. AP was responsible for preparing the figures in the manuscript. FJ, NS, SD, AP, and CM assisted in revising the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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