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Review Article

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Exploring the macin family of antimicrobial peptides: structure, function, and emerging applications in food safety

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Abstract

Rising levels of antimicrobial resistance (AMR) among foodborne pathogens is an increasing threat to food safety and product quality, driving the search for effective natural alternatives to conventional preservatives. Antimicrobial peptides (AMPs) have emerged as promising candidates for food preservation because of their broad-spectrum activity, diverse mechanisms of action and lower propensity for resistance development. Within this group, the macin family represents a promising yet underexplored class of cysteine-rich AMPs characterised by eight conserved cysteine residues that form four disulfide bonds. Macins have been identified across diverse taxa, including leeches, bivalves, gastropods, and hydrozoans and exhibit diverse antimicrobial mechanisms ranging from bacterial aggrelgation mediated by hydrophobic and electrostatic interactions and membrane permeabilization. This review provides a comprehensive synthesis of current knowledge of the macin family within the broader landscape of AMPs, highlighting their structural diversity, mechanisms of action and potential applications. Collectively, these characteristics suggest that macins may represent promising candidates for controlling resistant foodborne pathogens while maintaining product quality.

Impact Statement

This review highlights macins as an underexplored family of antimicrobial peptides (AMPs) with promising activity against foodborne pathogens. By consolidating current knowledge, it provides a foundation for evaluating their potential in food preservation and antimicrobial research.

Keywords Antimicrobial peptides, food antimicrobials, food safety, novel antimicrobials, activity

Introduction

The prolonged and widespread use of conventional antimicrobials across clinical, agricultural, and food industries, has contributed to the alarming rise of antimicrobial resistance (AMR) (Brul and Coote 1999, Manyi-Loh *et al*. 2018, WHO 2019, Murray *et al*. 2022, Liu *et al*. 2024, Zheng *et al*. 2024, Elbehiry *et al*. 2025). Within the food industry, antimicrobial-resistant foodborne pathogens pose significant threats to both food safety and public health (Liu *et al*. 2024, Zheng *et al*. 2024). Evidence indicates that foods of animal and aquatic origin can act as reservoirs for antimicrobial-resistant bacteria. For example, multidrug-resistant *Salmonella* and *Escherichia coli* harbouring clinically relevant resistance genes, such as *mcr-1*, have been detected in retail meat products, highlighting the AMR hazards spread across the food chain (Nhung *et al*. 2018, Tang *et al*. 2022). Similarly, antimicrobial-resistant bacterial strains have been isolated from frozen fruits, vegetables, and meat products (Al-Kharousi *et al*. 2016, Vojkovská *et al*. 2017). These foodborne pathogens encompass a wide range of bacteria, including *Vibrio parahaemolyticus* and *Vibrio cholera* (Bacon *et al*. 2003, Ma *et al*. 2014), *E. coli*, *S. typhi* and *S. paratyphi* (Scallan *et al*. 2011, Viazis *et al*. 2025), and *Staphylococcus aureus* (Bacon *et al*. 2003, Bintsis 2017).

To control spoilage and pathogen proliferation, synthetic chemical preservatives have long been incorporated into meat and related food products. However, their continued use has raised concerns about potential toxicity and promotion of AMR (Piper 2011, Mohammadzadeh-Aghdash *et al*. 2019, Recoules *et al*. 2025, Hasenböhler *et al*. 2026). Chemical preservatives, such as weak organic acids, exert antimicrobial effects by disrupting membrane integrity and intracellular pH homeostasis (Freese *et al*. 1973, Bracey *et al*. 1998). Prolonged exposure to these compounds can promote resistance through intrinsic and inducible responses, such as reduced membrane permeability, enzymatic degradation,

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and stress response pathways such as acid tolerance (Baik *et al*. 1996, Perri *et al*. 2020, Nazir *et al*. 2025). These adaptive responses may also confer cross-protection against other antimicrobials (García-Penas *et al*. 2026). Consequently, there is growing interest in the use of nature-derived antimicrobial compounds as safer and more sustainable alternatives for controlling foodborne pathogens and mitigating AMR (Lee *et al*. 2021, Purgatorio *et al*. 2022, Woo *et al*. 2023, Dong *et al*. 2024). Among the natural antimicrobial agents investigated to date, promising candidates for food preservatives include bacteriocins of microbial origin (da Costa *et al*. 2019), plant-derived extracts (Ceruso *et al*. 2020), chitosan derived from marine crustaceans (Kanatt *et al*. 2008), and more recently, insect-derived chitosan (Triunfo *et al*. 2026).

Antimicrobial peptides (AMPs) represent a promising class of naturally derived antimicrobial agents with considerable potential as alternatives to conventional chemical preservatives (Singh *et al*. 2024). AMPs are widely distributed among animals, plants, and microorganisms where the function as key components of innate immune defence against potentially harmful microbes (Zasloff 2002, Jenssen *et al*. 2006, De Stefano *et al*. 2026). Microorganisms and AMPs have co-evolved over hundreds of millions of years, yet AMPs have retained potent antimicrobial activity, while many pathogens have shown only limited capacity to evade their lethal effects (Pasupuleti *et al*. 2012). Most organisms produce diverse AMP repertoires that collectively provide broad-spectrum antimicrobial defence, although individual peptides often display selective activity against specific groups of microorganisms, including bacteria, fungi, viruses and parasites (Bahar and Ren 2013, Zhang *et al*. 2021, Erdem and Kesmen 2022), This selectivity, combined with their broad antimicrobial potential, has made AMPs attractive candidates for food preservation (Corbalán *et al*. 2021, Dell'Olmo *et al*. 2021, Dong *et al*. 2022).

Although resistance to individual AMPs can arise under *in vitro* conditions, the simultaneous activity of multiple peptides within natural host defence systems is thought to constrain the development of effective resistance mechanisms. Consequently, AMPs are generally considered less likely to induce resistance or mutagenesis compared with conventional antimicrobials. Nevertheless, AMP-resistant strains can emerge under intensive laboratory selection, and certain bacterial adaptations, such as capsule formation, may reduce susceptibility to AMP-mediated killing (Campos *et al*. 2004, Nizet 2006).

The application of AMPs in food preservation has attracted increasing research interest in recent years. Compared with conventional preservatives, AMPs offer several advantages, including their natural origin, relatively lower toxicity, biodegradability, and reduced propensity to promote microbial resistance (Pasupuleti *et al*. 2012, Younes *et al*. 2017). A numbers of AMPs, including Enterocin (Kasimin *et al*. 2022) and Lactoferricin (Demir *et al*. 2025), have been classified by the U.S. Food and Drug Administration (FDA) as 'Generally Regarded as Safe' (GRAS) and are currently being explored as food additives. Others, such as Nisin (Hanchi *et al*. 2018, Field *et al*. 2023), Natamycin (Meena *et al*. 2021), Pediocin PA-1 (Espitia *et al*. 2025) and ε-Polylysine (Hiraki *et al*. 2003), are already approved as food preservatives because of their demonstrated antimicrobial efficacy, and environmental stability and safety profiles (Younes *et al*. 2017).

AMPs exert antimicrobial activity through a diverse range of mechanisms, most commonly involving disruption of microbial membranes via pore formation or detergent-like micellization (Gallo *et al*. 2002, Zasloff 2002, Jenssen *et al*. 2006, Moretta *et al*. 2021). Three principal models have been proposed to explain AMP-mediated permeabilization; the barrel-stave model, the toroidal-pore model, and the carpet model. In the barrel-stave and toroidal-pore models, peptides insert into the membrane to form stable or transient pores, depending on peptide concentration and membrane composition. In contrast, the carpet model involves peptides aligning parallel to the membrane surface until a threshold concentration is reached, leading to micellization and membrane disintegration (Raheem and Straus 2019). The extensive membrane damage induced by many AMPs is generally considered too complex for bacteria to readily overcome through resistance adaptions, further supporting their potential for medical and industrial applications (Schwab *et al*. 1999, Meng *et al*. 2010, Otero-Gonzáiez *et al*. 2010, Jung *et al*. 2011, Neonakis *et al*. 2011). In addition to membrane disruption, some AMPs inhibit the synthesis of cellular components, For example, several peptides target lipid II, a critical precursor in peptidoglycan (PGN) biosynthesis, resulting in the inhibition of cell wall formation (Brötz *et al*. 1997, Wilmes *et al*. 2011). Other AMPs can translocate across microbial membranes and accumulate intracellularly, where they interfere with nucleic acid synthesis, protein synthesis, enzymatic activity and other essential cellular processes (Jenssen *et al*. 2006).

Individual organisms frequently produce multiple AMP-related proteins with overlapping but distinct functional properties. Within this diverse AMP landscape, the macin family of antimicrobial proteins has emerged as a distinct and potentially important group exhibiting strong activity against several major foodborne pathogens, including *S. aureus* (Du *et al*. 2023), *E. coli* (Jung *et al*. 2009, Du *et al*. 2023, Dong *et al*. 2024, Hu *et al*. 2025), *V. parahaemolyticus* (Yang *et al*. 2019, Dong *et al*. 2024, Hu *et al*. 2025) and *S. typhimurium* (Dong *et al*. 2024). Despite being identified almost two decades ago, the macin family remains critically underrepresented within the broader AMP literature (Gerdol and Venier 2015). This review therefore aims to consolidate current knowledge of macin-related antimicrobial proteins, providing a foundation for future research into their potential applications in combating AMR and improving food safety.

AMPs: Macins

Macins constitute a distinct family of AMPs identified primarily in annelids, molluscs, and cnidarians (Tasiemski *et al*. 2004, Schikorski *et al*. 2008, Tasiemski 2008, Gerdol *et al*. 2012, Jung *et al*. 2012, Yang *et al*. 2016, Hu *et al*. 2025). The absence of adaptive immunity in these taxa necessitates a heavy reliance on highly diverse innate immune systems to survive the extreme and fluctuating environmental conditions characteristic of their habitats. As a result, these ancient lineages represent an extensive reservoir of structurally and functionally diverse AMPs (Kawsar *et al*. 2025).

The earliest identified and characterised members of the macin family, theromacin, neuromacin, and hydramacin, share a conserved structural foundation that has since been recognised across subsequent discovered macins. All three peptides exhibit membrane-permeabilizing activity, however important functional differences have also been reported. Both hydramacin and neuromacin induce bacterial aggregation, whereas theromacin lacks this property. Neuromacin additionally displays the strongest

membrane-permeabilizing capacity and is uniquely capable of forming membrane pores (Jung *et al*. 2012).

Macins are synthesised as secreted precursor peptides characterized by a highly conserved cysteine scaffold typically comprising eight cysteine residues, although some "long" macins, including theromacin, possess an additional cysteine pair (Jung *et al*. 2012, Egessa 2022). Despite this conserved cysteine architecture, macins display considerable functional diversity, likely influenced by variation in charged and non-conserved amino-acid residues (Jung *et al*. 2009, 2012, Hung *et al*. 2014). Collectively, macins exhibit broad antimicrobial potential, although individual peptides vary substantially in both antimicrobial spectrum and potency. Many macins display primarily antibacterial activity, with differing efficacy against Gram-positive and Gram-negative bacteria (Jung *et al*. 2012, Lv *et al*. 2019, Jiao *et al*. 2024, Zhang *et al*. 2025), while others additionally demonstrate anti-yeast activity (Xue *et al*. 2021). Macins are generally thought to initiate their bactericidal activity through bacterial aggregation (Jung *et al*. 2009, 2012). Following this initial interaction, secondary effects may involve membrane permeabilization, pore formation and associated alterations in cell morphology, ultimately leading to microbial cell death (Jung *et al*. 2012).

Hydramacin-1

The metazoan *Hydra* is among the simplest extant multicellular organisms. Despite its morphological simplicity, the *Hydra* epithelium produces a diverse array of potent AMPs that provide protection against pathogenic bacteria (Augustin *et al*. 2009, Bosch *et al*. 2009). As an organism that relies exclusively on innate immunity while inhabiting microbe-rich freshwater environments, Hydra has emerged as an important model for studying AMPs. The induction of these AMPs is regulated through interactions between a leucine-rich repeat (LRR)-containing protein and a Toll/interleukin-1 receptor (TIR)-domain-containing protein lacking LRR motifs, together forming a receptor complex functionally analogous to the Toll-like receptors of higher animals. Evidence for this interaction is supported by both *in vitro* studies demonstrating activation of downstream signalling pathways and *in vivo* observations in *Hydra*, although some mechanistic remain inferred from similarities with Toll-like receptor systems in higher organisms. One of the AMPs regulated downstream of this TIR/LRR signalling complex is Hydramacin-1 (HM1), a cationic AMP with well-established bactericidal activity against both Gram-positive and Gram-negative bacteria (Bosch *et al*. 2009). HM1 exhibits an unusual and extensively studied mechanism of action referred to as the '*barnacle model*' (Jung *et al*. 2009). This mechanism is linked to the distinctive molecular surface properties of the peptide, which comprises two hydrophobic hemispheres separated by a belt of positive charges. Such structural organisation (Fig. 1) enables HM1 to induce bacterial aggregation through simultaneous electrostatic and hydrophobic interactions with the membranes of adjacent bacterial cells. In this model, individual bacterial cells become cross linked by peptide-mediated membrane interactions, allowing the formation of large cellular aggregates under certain conditions (Michalek *et al*. 2013). Expression of HM1 has been localised to the endodermal epithelium of *Hydra*. Jung *et al*. (2009) demonstrated the membrane-permeabilizing activity of HM1 using *Bacillus megaterium* at a concentration of 10^6 cells ml^{-1}, with ~50% permeabilization achieved at peptide concentrations of 5 $\mu g\ ml^{-1}$. *In vitro*, HM1 displayed particularly strong antimicrobial activity against several Gram-negative bacteria, including *Citrobacter freundii* (C7), *Enterobacter cloacae* (Va12270/03), *E. coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *S. typhimurium*, and *Yersinia enterolitca* (Table S1; Supplementary Material). Among Gram-positive bacteria, the highest bactericidal activity was reported against *Staphylococcus hemolyticus* (Bosch *et al*. 2009, Jung *et al*. 2009).

Importantly, HM1 was the first member of the macin family shown to mediate bacterial aggregation through membrane cross-linking, thereby revealing a previously undescribed antimicrobial mechanism within this AMP family (Jung *et al*. 2009). Aggregation occurs at sub-minimum bactericidal concentrations (sub-MBC levels) and is thought to arise from the peptide's dual amphipathic character, whereby its hydrophobic domains bind bacterial membranes and initiate cell-cell adhesion. Although first described for HM1, similar aggregation-mediated antimicrobial activity has subsequently been reported for other macins, including neuromacin (Jung *et al*. 2009, Michalek *et al*. 2013). Following exposure, bacterial cells develop electron-dense contact regions accompanied by pronounced morphological alterations, resulting in a characteristic thorn apple-like appearance marked by surface protrusions. Subsequent membrane permeabilization and structural disruption ultimately lead to bacterial cell death (Jung *et al*. 2009).

Neuromacin

Neuromacin, isolated from the leech *Hirudo medicinalis* (Table 1) (Schikorski *et al*. 2008), shares notable sequence similarity with HM1 (61% pairwise sequence similarity; BLASTp (NCBI) calculated based on the highest-scoring alignment). Similar to HM1, neuromacin possesses a ringlike arrangement of cationic residues flanked by two opposing hydrophobic regions, consistent with the proposed barnacle model of action. Accordingly, neuromacin binds to and cross-links bacterial cell surfaces, resulting in cellular aggregation. However, compared to HM1, neuromacin exhibits markedly greater cytoplasmic membrane permeabilization against *B. megaterium* (i.e. 50% permeabilization at 0.2–0.6 versus 2–6 $\mu mol\ l^{-1}$ with HM1 for a comparable effect). Among the three macins investigated (HM1, neuromacin and theromacin), pore-forming activity was observed exclusively for neuromacin (Jung *et al*. 2012). Neuromacin also displayed potent antibacterial activity against *B. megaterium* and *S. aureus,* with minimum bactericidal concentrations (MBCs) of 0.20 and 6.25$\mu g\ ml^{-1}$, respectively (Table S1) (Jung *et al*. 2012).

The pore-forming activity of neuromacin has been hypothesized to arise from protonation and de-protonation of specific histidine residues that are notably absent in HM1 and theromacin. In addition to its antimicrobial properties, neuromacin has also been implicated in neural regeneration, where it promotes repair of leech nerve tissue (Schikorski *et al*. 2008). Neuromacin also enhanced the survival of murine neuroblastoma cells, suggesting broader neuroprotective functions. Expression analyses further revealed that neuromacin is localized within both microglial cells and neurons of the leech nervous system (Jung *et al*. 2012). However, the pore-forming activity of neuromacin is relatively moderate compared to the classical pore-forming peptide alamethicin, requiring concentrations ~20 times higher to achieve 50% pore formation (2 verses 0.1 $\mu mol\ l^{-1}$ for alamethicin).

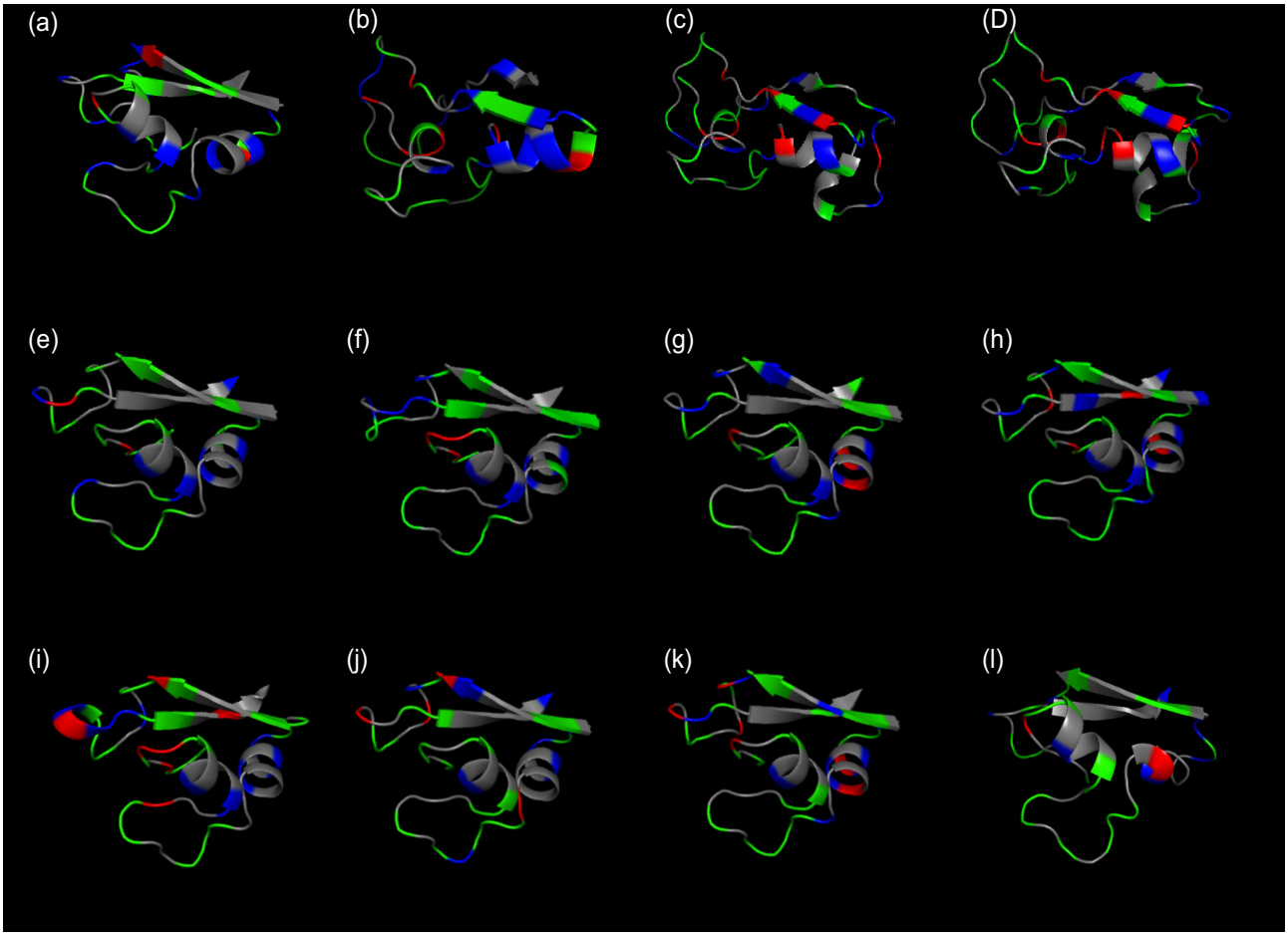

Figure 1 Predicted 3D structures of selected macin-family peptides, highlighting hydrophobic regions (green), negatively charged regions (red) and positively charged regions (blue). Structural models were generated by the authors using SWISS-MODEL and visualized in PyMOL. (a) HM1. (b) Neuromacin. (c) Theromacin *Hm* (from *H. medicinalis*). (d) Theromacin *Tt* (from *T. tessulatum*). (e) Theromacin *Sc* (from *S. constricta*). (f) Mytimacin-1. (g) Mytimacin-2. (h) Mytimacin-3. (i) Mytimacin-4. (j) Mytimacin-5. (k) Mytimacin-6. (l) P*f*Macin1. The NMR structure of HM1 was used as the modelling template for all macins except neuromacin and theromacin *Tt*, for which the NMR structure of theromacin Hm served as the structural template.

Hirudomacin

Hirudomacin (Hmc), identified in the salivary gland of the leech *Hirudo nipponica* is another member of the macin family whose primary structure shares ˜45.8%–90.1% amino acid sequence similarity with HM1 and theromacin *Tt*, respectively (Fig. 2) (Table 2). The mature peptide exhibited strong antimicrobial activity against *Bacillus subtilis* and *S. aureus*, with MBCs of 0.39 and 1.56 μg ml^{-1}, respectively (Table S1). Transmission electron microscopy (TEM) and structural analyses indicated that the antimicrobial activity of Hmc is dependent on the combined effects of its cationic and amphipathic properties. These features facilitate electrostatic interactions with negatively charged bacterial membranes, leading to membrane permeabilization and subsequent bacterial cell lysis (Ding *et al*. 2019). *In vitro*, Hmc also exhibited strong antimicrobial activity against *S. aureus* and *E. coli*, with MIC values of 0.39 and 1.56 μg ml^{-1}, respectively (Table S1) (Ding *et al*. 2019, Du *et al*. 2023). Consistent these findings, administration of Hmc at its MIC reduced bacterial burden by approximately 50% *in vivo* in *C. elegans* infected with either *S. aureus* or *E. coli* (Ding *et al*. 2019). Expression profiling further revealed that Hmc transcripts were most abundant in the salivary glands and intestine, with lower expression detected in the skin and gonad tissues (Ding *et al*. 2019). Recent comparative genomic analyses also identified multiple hirudomacin-like macin homologues in medicinal leeches, suggesting that hirudomacin belongs to a broader multigene family with differential expression and varying degrees of functional conservation (Yu *et al*. 2025).

Theromacin

Theromacin, first identified in the leech *Theromyzon tessulatum* (Table 2), shares considerable sequence similarity with neuromacin and similarly exhibits neuroregenerative properties, including promotion of nerve repair and enhanced viability of neuroblastoma cells in murine models. Expression of theromacin was reported primarily in large fat cells associated with the coelomic cavities (Tasiemski *et al*. 2004). Similar to neuromacin, theromacin homologs identified in *Hirudo medicinalis* displayed strong antimicrobial activity against *B. megaterium* (MBC=0.39 μg ml^{-1}) (Jung *et al*. 2012) (Table S1). However, unlike HM1 and neuromacin, theromacin did not induce bacterial aggregation (Boidin-Wichlacz *et al*. 2012, Jung *et al*. 2012). Based on limited bacterial isolates tested, both theromacin and neuromacin appeared to

Table 1 A qualitative overview of the reported spectrum of characterized macins across phylogenetically diverse taxa. *Spectrum* indicates whether activity has been reported against Gram-positive bacteria (Gm +ve), Gram-negative bacteria (Gm−ve), and/or fungi (F). *Preference* denotes relatively stronger reported activity, whereas *Broad* indicates activity against both bacterial groups without a clear reported preference. These classifications summarize comparative trends in activity rather than quantitative potency. Detailed quantitative antimicrobial data, including MIC and/or MBC values, are provided in Table S1, Supplementary Material.

Phylum/species	Macin	Antimicrobial spectrum	Preference	References
Cnidaria				
Hydra	Hydramacin	Gm +ve and Gm −ve	Broad	(Jung *et al*. 2012)
Annelida				
Hirudo medicinalis	Neuromacin	Gm +ve and Gm −ve	Gm +ve favoured	(Jung *et al*. 2012)
Hirudo nipponia Whitman	Hirudomacin	Gm +ve and Gm −ve	Gm +ve favoured	(Ding *et al*. 2019, Du *et al*. 2023)
Theromyzon tessulatum	Theromacin	Gm +ve and Gm −ve	Broad	(Tasiemski *et al*. 2004, Jung *et al*. 2012)
Perinereis linea	Theromacin	Gm +ve and Gm −ve	Broad	(Joo *et al*. 2020)
Mollusca				
Sinonovacula constricta	Theromacin	Gm +ve and Gm −ve	Broad	(Hu *et al*. 2025)
Mytilus galloprovincialis	Mytimacin-4	Gm +ve and Gm −ve	Gm −ve favoured	(Lv *et al*. 2019, Dong *et al*. 2024)
Venerupisphilippinarum	VpMacin	Gm +ve and Gm −ve	Gm −ve favoured	(Yang *et al*. 2019)
	VpMacin-1	Gm +ve, Gm −ve and F	Gm −ve favoured	(Xue *et al*. 2021)
	VpMacin-2	Gm +ve, Gm −ve and F	F favoured	(Xue *et al*. 2021)
Pinctada fucata	*Pf*Macin1	Gm +ve and Gm −ve	Gm −ve favoured	(Zhang *et al*. 2025)
Haliotis discus hannai	HdMac	Gm +ve and Gm −ve	Gm −ve favoured	(Jiao *et al*. 2024)

exhibit preferential antimicrobial activity against Gram-positive bacteria (Table 1) (Tasiemski *et al*. 2004, Jung *et al*. 2012).

A theromacin homolog identified in the polychaete *Perinereis linea* (Table 2) displayed a broader antimicrobial spectrum and was predominantly expressed in the head region. Synthetic theromacin inhibited the Gram-positive bacterium *Streptococcus iniae* (MIC=31.3 μg ml^{-1}) and several Gram-negative *Vibrio* species, including *V. ordalii*, *V. alginolyticus*, and *V. campbellii* with MICs of 1.0, 7.8, and 15.6 μg ml^{-1}, respectively (Joo *et al*. 2020). However, some Gram-negative species, such as *Edwardsiella piscicida* and *V. harveyi,* exhibited substantially lower susceptibility (MIC=62.5 μg ml^{-1}) (Table S1). The broader Gram-negative activity observed for the *P. linea* theromacin homolog, relative to earlier findings in *H. medicinalis*, may reflect differences in peptide sequence and physicochemical properties. Additionally, the relatively narrow range of Gram-negative bacterial isolates tested in earlier studies may have underestimated the antimicrobial spectrum of theromacin peptides.

Although the antimicrobial mechanisms of theromacin remained unresolved in earlier studies (Schikorski *et al*. 2008, Jung *et al*. 2012), more recent work by Hu *et al*. (2025) proposed that theromacin from the razor clam *Sinonovacula constricta* exerts activity through binding to lipopolysaccharide (LPS) on Gram-negative bacterial surfaces. Consistent with this mechanism, the recombinant peptide displayed potent activity against several Gram-negative species, including *E. coli*, *Vibrio splendidus*, *V. parahaemolyticus*, and *Vibrio anguillarum* (MICs=0.42, 0.64, 0.64, 0.32 μg ml^{-1}, respectively) (Table S1). Expression of theromacin in *S. constricta* was highest in gonad tissues, followed by foot, hepatopancreas, adductor muscle and gills, broadly consistent with tissue expression patterns reported in *P. linea* (Joo *et al*. 2020). In addition to membrane interactions, theromacin was shown to bind and aggregate genomic DNA from *V. parahaemolyticus,* suggesting that intracellular bacterial DNA may represent an additional target alongside the bacterial membrane (Hu *et al*. 2025).

Mytimacins

Transcriptomic analysis of the Mediterranean mussel *Mytilus galloprovincialis* identified five mRNAs encoding members of the macin family, designated mytimacins one to five (Gerdol *et al*. 2012) (Table 2). All five proteins retain the eight conserved cysteine residues characteristic of macins and predicted to form four intramolecular disulfide bridges. However, mytimacins one, four, and five contain two additional cysteine residues that may facilitate formation of a fifth disulfide bond, a structural feature previously associated with longer theromacin-like peptides (Fig. 2) (Tasiemski *et al*. 2004, Joo *et al*. 2020, Hu *et al*. 2025). In contrast, mytimacins two and three lack this C-terminal extension and are therefore structurally more similar to HM1 and neuromacin (Schikorski *et al*. 2008, Jung *et al*. 2009). Consistent with this relationship, the predicted tertiary structure of mytimacin-3 (Fig. 1) exhibited a high degree similarity to HM1, sharing 64.4%

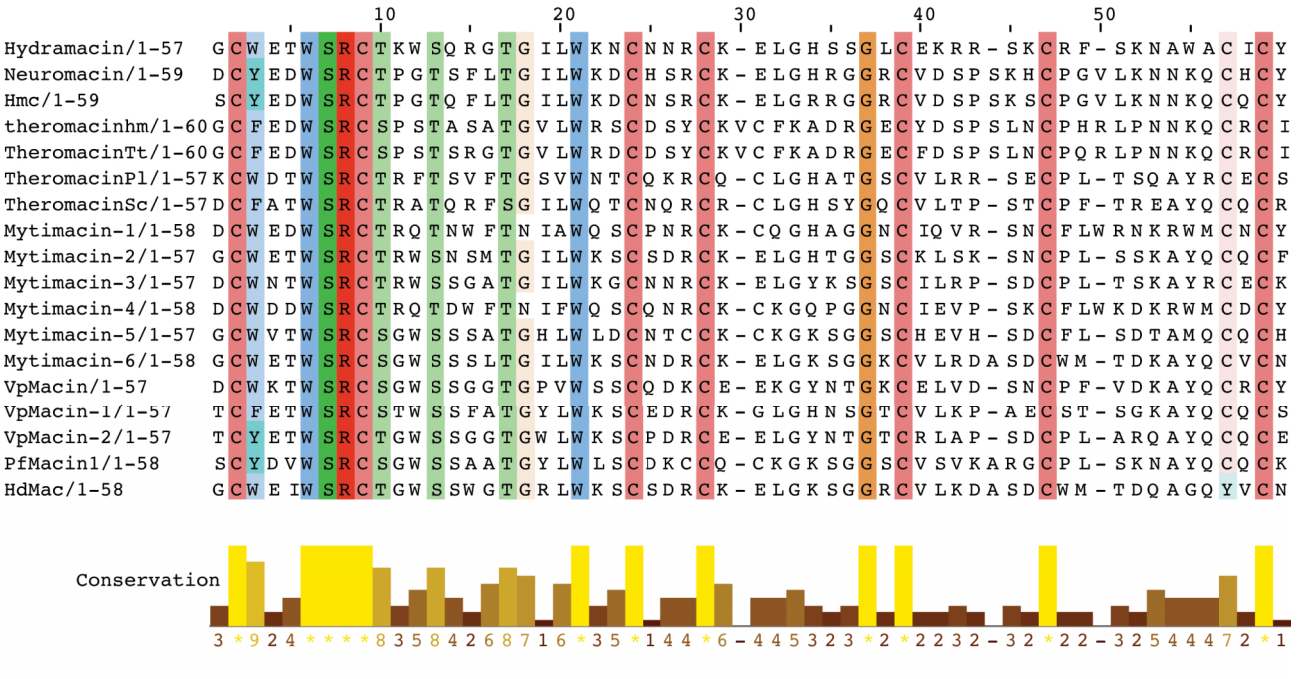

Figure 2 Multiple sequence alignment of selected macin-family peptides. The shaded regions indicate ≥40% amino acid conservation. The sequences analysed were hydramacin (AFQ20833.1), neuromacin (ABW97519.1), hirudomacin (*Hmc*) (QBK51064.1), theromacin *Hm* (from *H. medicinalis*) (ABV56569), theromacin *Tt* (from *T. tessulatum*) (AAR12065.1), theromacin *Pl* (from *P. linea*) (QAU32334.1), theromacin *Sc* (from *S. constricta*) (PDB: XOI27391.1), mytimacin-1(CCC15015.1), mytimacin-2 (CCC15016.1), mytimacin-3 (CCC15017.1), mytimacin-4 (CCC15018.1), mytimacin-5 (CCC15019.1), mytimacin-6 (QHI06026.1), VpMacin (APY18888.1), VpMacin-1 (APY18887.1), VpMacin-2 (APY18889.1), *pf*Macin1 (XZP61820.1) and HdMac (PDB: WNY63410.1). Sequence alignment was performed using MEGA12 and Jalview software. The Clustal X colour scheme was applied to highlight cysteines in pink, hydrophobic residues in blue, polar residues in green, positive residues in red and glycines in orange.

sequence identity. Conserved lysine and arginine residues forming a positively charged surface belt, considered central to the antimicrobial activity of HM1, were also identified in the mytimacins, further supporting their classification as candidate AMPs (Jung *et al*. 2009, Gerdol *et al*. 2012).

Expression profiling further suggests functional diversification within the mytimacin family. Mytimacin-1 was most highly expressed in the digestive gland of *M. galloprovincialis*, followed by posterior adductor muscle, foot, mantle and gills, with comparatively low expression in hemocytes. Mytimacin-2 expression was concentrated primarily in the gills and, to a lesser extent, the foot, whereas mytimacin-3 was predominantly expressed in mantle tissues. In contrast, mytimacin-4 showed highest expression in the posterior adductor muscle, followed by hepatopancreas, gonads, hemocytes, mantle and gills. The differential expression of mytimacins across tissues suggests functional diversification within the family, with individual peptides likely produced by specialised cell populations and adapted to distinct tissue-specific roles (Gerdol *et al*. 2012).

To date, antimicrobial activity has only been experimentally validated for mytimacin-4, while the biological activities of the remaining mytimacins remain largely unexplored (Lv *et al*. 2019). Recombinant mytimacin-4 exhibited inhibitory activity against both Gram-positive and Gram-negative bacteria, including *B. subtilis* and *V. parahaemolyticus* with MICs of 0.315 and 0.62 μmol l^{-1}, respectively (Lv *et al*. 2019). More recently, Dong *et al*. (2024) employed a *Pichia pastoris* expression system to further investigate the antibacterial properties, mechanism of action, and potential food preservation applications of mytimacin-4. Consistent with earlier findings, mytimacin-4 displayed greater activity against Gram-negative bacteria than Gram-positive species, likely reflecting differences in cell envelope structure and composition (Lv *et al*. 2019, Dong *et al*. 2024). *E. coli*, *S. typhimurium* and *Pseudomonas aeruginosa* were relatively sensitive to mytimacin-4, with MICs of 15, 20, and 25 μg ml^{-1}, respectively, whereas, *Listeria monocytogenes* and *B. subtilis* displayed moderate to low susceptibility (MICs=45 and 65 μg ml^{-1}, respectively) and *S. aureus* was insensitive to the peptide (Table S1) (Dong *et al*. 2024). Mechanistic investigations demonstrated that mytimacin-4 disrupts membrane integrity, induces intracellular structural damage and binds bacterial DNA, with cell wall rupture and shrinkage observed at 2×MIC, supporting a bactericidal mode of action. Consistent with findings for the theromacin homolog in *P. linea* (Joo *et al*. 2020), mytimacin-4 shares several features with theromacin, including the presence of two additional cysteine residues and DNA-binding activity (Jung *et al*. 2012, Dong *et al*. 2024, Hu *et al*. 2025).

An additional macin-like peptide, mytimacin-6 (referred to here as Hd-mtmc 6), was identified in the small abalone *Haliotis diversicolor* (Xie *et al*. 2021, Table 2). Hd-mtmc 6 possesses structural features closely resembling those of HM1 (Fig. 1) and is therefore also predicted to exhibit AMP activity, although this remains to be experimentally validated. Expression in *H. diversicolor* tissues

Table 2 Species origin, sequence characteristics and predicted physicochemical properties of characterized macins from aquatic organisms. Values of theoretical pI, aliphatic index, GRAVY and molecular mass were predicted using ExPASy ProtParam tool (Gasteiger *et al*. 2005) Theoretical pI, Theoretical isoelectric point, GRAVY, Grand average of hydropathicity, ND, Not Detected.

Macin	Species	Number of cysteine residues	Theoretical pI	Aliphatic index	GRAVY	Molecular mass (kDa)	Ref.	Accession number
HM1	*Hydra vulgaris*	8	9.53	70.00	−0.119	9.7	(Jung *et al*. 2009, Egessa 2022)	JX118848
Neuromacin	*Hirudo medicinalis*	8	8.41	68.90	−0.112	9.3	(Schikorski *et al*. 2008, Jung *et al*. 2012)	EU156754
Hirudomacin	*Hirudo nipponia* Whitman	8	8.81	77.20	−0.066	9.2	(Ding *et al*. 2019, Du *et al*. 2023)	MH686152
Theromacin	*Hirudo medicinalis*	10	8.60	36.53	−0.764	8.5	(Jung *et al*. 2012)	EU149766
	Theromyzon tessulatum	10	8.49	63.40	−0.281	10.8	(Tasiemski *et al*. 2004)	AY434032
	Perinereis linea	10	9.25	58.64	−0.030	11.4	(Joo *et al*. 2020)	MH181386
	Sinonovacula constricta	10	9.13	72.55	0.098	10.9	(Hu *et al*. 2025)	PQ818121
Mytimacin-1	*Mytilus galloprovincialis*	10	9.01	65.64	−0.227	11.5	(Gerdol *et al*. 2012)	FR873274
Mytimacin-2		8	8.81	59.46	−0.136	9.9		FR873275
Mytimacin-3		8	8.97	68.94	−0.005	9.4		FR873276
Mytimacin-4		10	8.01	64.65	−0.192	11.6	(Gerdol *et al*. 2012, Lv *et al*. 2019)	FR873277
Mytimacin-5		10	8.00	51.70	−0.008	11.5	(Gerdol *et al*. 2012)	FR873278
Mytimacin-6	*Haliotis diversicolor*	8	8.47	70.62	−0.057	9	(Xie *et al*. 2021)	MK358139
VpMacin	*Venerupis philippinarum*	9	8.08	58.64	−0.189	9.7	(Yang *et al*. 2019)	KX454482
VpMacin-1		8	8.69	74.59	0.200	9.3	(Xue *et al*. 2021)	KX454481
VpMacin-2		9	5.18	74.59	0.051	9.5		KX454483
PfMacin1	*Pinctada fucata*	8	9.30	52.00	−0.085	11.4	(Zhang *et al*. 2025)	XZP61820.1
HdMac	*Haliotis discus hannai*	7	8.56	67.00	−0.094	8.97	(Jiao *et al*. 2024)	OR539713

was highest in the mantle, followed by in head, foot, gill and hepatopancreas (Xie *et al*. 2021).

VpMacins

Additional macin-family AMPs have been identified in members of the clam genus *Venerupis* (Yang *et al*. 2019) (Table 2). One such peptide, VpMacin, displayed greater activity against Gram-negative than Gram-positive bacteria, with MICs values ranging from 1.0 to 8.0 μmol l^{-1} for the Gram-negative species examined (Table S1). Notably, *V. parahemolyticus* was highly susceptible (MIC=1 μmol l^{-1}), whereas Gram-positive bacteria required higher concentrations for inhibition (8 to 16 μmol l^{-1}) (Yang *et al*. 2019). Although VpMacin lacks the two additional cysteine residues characteristic of theromacin-like peptides, it exhibits several comparable functional properties, including increased membrane permeability mediated through binding to LPS, PGN, and glucan, ultimately resulting in membrane disruption, morphological alterations and bacterial cell death (Yang *et al*. 2019, Hu *et al*. 2025). Quantitative RT-PCR analyses revealed that VpMacin transcripts were predominantly expressed in the gills, followed by in hepatopancreas, hemocytes, mantle and to lesser extent, muscle tissues. Expression was also significantly upregulated following bacterial challenge with *V. anguillarum*, supporting a role in host immune defence (Yang *et al*. 2019, Xue *et al*. 2021) identified two additional macin-type AMPs, VpMacin-1, and VpMacin-2, in the Manila clam *V. philippinarum* (Table 2). Both peptides were primarily expressed in the gills and hepatopancreas and were significantly upregulated following *V. anguillarum* infection, further supporting their involvement in host innate immunity. Recombinant VpMacin-2 displayed stronger activity against Gram-negative bacteria, with MICs approximately four-fold lower than those observed for Gram-positive strains (Table S1). Both peptides were active against *V. harveyi* and *V. splendidus*, whereas VpMacin-2 displayed a broader antimicrobial spectrum against additional *Vibrio* species and demonstrated greater inhibition of bacterial biofilm formation (Xue *et al*. 2021). Notably, VpMacin-1, and VpMacin-2 exhibited antimicrobial activity against both bacterial and fungal strains (Xue *et al*. 2021), whereas the previously characterized VpMacin had only been evaluated for antibacterial activity (Yang *et al*. 2019). As the antifungal activity was not assessed for VpMacin, direct comparisons of the antifungal spectra between these peptides are not possible. In addition, VpMacin-1 and VpMacin-2 displayed strong dose-dependent binding affinities to the pathogen-associated microbial patterns (PAMP) substrates zymosan and chitin in Enzyme-Linked Immunosorbent As-

say (ELISA). These substrates served as *in vitro* model ligands for assessing microbial recognition properties and should not be interpreted as evidence that chitin represents a physiological bacterial target (Yang *et al*. 2019, Xue *et al*. 2021).

P*f*Macin1

P*f*Macin1, identified from the pearly oyster *Pinctada fucata*, is the most recently characterized member of the macin family. Expression analyses revealed that P*f*Macin1 is predominantly expressed in the mantle and is upregulated in the hemolymph, gills and mantle following challenge with *S. aureus* and *V. alginolyticus*, supporting a role in antimicrobial defence (Table 2) (Zhang *et al*. 2025). Recombinant P*f*Macin1 exhibited strong antimicrobial activity against both Gram-negative and Gram-positive bacteria at relatively low concentrations, although Gram-positive strains displayed comparatively lower susceptibility (Table S1). The proposed mechanism of action involves direct binding to bacterial cells followed by disruption of cell membrane integrity. Scanning electron microscopy revealed pronounced morphological alterations in treated cells, including marked membrane deformation and cellular shrinkage. P*f*Macin1 selectively binds lipoteichoic acid and LPS but not PGN, a binding profile that may contribute to its enhanced activity against Gram-negative bacteria. However, interpretation of these findings remain limited by the relatively small number of bacterial species evaluated and the absence of *in vivo* validation studies (Yang *et al*. 2019).

HdMac

Jiao *et al*. (2024) identified a novel macin-family peptide, HdMac, in Pacific abalone *Haliotis discus hannai* (Table 2). Similar to theromacin and Vpmacin-2, HdMac exhibited potent antibacterial activity against *V. anguillarum*, with an MIC of 1 μmol l^{-1} (Jiao *et al*. 2024) (Table S1) (Xue *et al*. 2021, Hu *et al*. 2025). In addition to its direct antibacterial activity, HdMac markedly inhibited biofilm formation by *E. coli*, even at low concentrations (0.1 MIC), possibly by reducing the initial attachment of bacterial cells or enhancing bacterial motility on the polystyrene surfaces. The proposed mechanisms of action of HdMac resembles that described for VpMacin by Yang *et al*. (2019), with the recombinant peptide capable of binding multiple PAMPs, including LPS, PGN, and glucan (Yang *et al*. 2019). Increased N-phenyl-1-naphthylamine fluorescence intensity in *E. coli* following exposure to HdMac further indicated that the peptide disrupts bacterial membrane integrity through permeabilization of the lipid membrane. Expression analyses revealed highest transcript abundance in hemocytes followed by in hepatopancreas, gills, mantle and muscle supporting a role in systemic innate immune defence (Jiao *et al*. 2024).

Sequence conservation in Macin peptides

Although AMPs from different organisms often share similar biophysical properties, sequence conservation is often very low, even among closely related species (Pasupuleti *et al*. 2012, Santos-Júnior *et al*. 2024). A recent large-scale analysis of the global microbiome highlighted the remarkable balance between sequence diversity and structural conservation that characterizes AMPs (Santos-Júnior *et al*. 2024). Examination of 863 498 putative AMPs from 63 410 genomes and metagenomes revealed that core structural motifs associated with membrane binding and microbial killing, including cationic residues, amphipathic regions, and disulfide bonds, were strongly conserved (Ilyas *et al*. 2019, Kumar *et al*. 2020, Bin Hafeez *et al*. 2021). In contrast, the surrounding regions were typically highly divergent (Santos-Júnior *et al*. 2024). Within the macin-family, these conserved structural features appear to be functionally critical. Conserved cysteine residues stabilize the tertiary structure required for biological activity, while the arrangement of cationic and hydrophobic residues facilitates interactions with microbial surfaces, promoting membrane binding and bacterial aggregation, as demonstrated for HM1 (Jung *et al*. 2009). Macins from phylogenetically diverse animals share a common structural framework centred on a conserved cysteine architecture, and conservation within this core region appears greater than that observed for many other AMP families (Fig. 2). The coexistence of conserved structural motifs with substantial sequence variation likely reflects evolutionary constraints that preserve core antimicrobial functionality while permitting diversification that may broaden microbial target specificity and facilitate adaptation to distinct microbial environments (Pasupuleti *et al*. 2012). Such patterns of conservation and diversification are characteristic of many AMP families and are thought to contribute to their long-term evolutionary persistence.

To further examine evolutionary relationships within the macin family, we explored phylogenetic relationships among representative macin peptides (Figure S1; Supplementary Material), revealing substantial sequence divergence across taxa. Bootstrap support values varied considerably throughout the phylogeny, with only a limited number of nodes showing strong support (>90%), whereas many deeper branches were poorly resolved. This likely reflects both the high sequence divergence among macins (average *p*-distance=0.746; Table S2) and the inherent difficulty of resolving evolutionary relationships among short, rapidly evolving peptide sequences. Moreover, the analysed sequences are not necessarily orthologous, as lineage-specific gene duplications followed by functional diversification may have contributed to the observed phylogenetic patterns. For example, although annelid-derived macin sequences did not form a single monophyletic clade, leech-derived sequences clustered separately from the more divergent polychaete homologs, suggesting substantial phylogenetic and potentially functional divergence within the phylum.

Bacterial resistance to AMPs

Although AMPs represent a promising strategy to combat AMR, microorganisms are nevertheless capable of evolving resistance to these compounds (Lai and Gallo 2009). Pathogenic bacteria employ a range of mechanisms to evade AMP-mediated killing, including proteolytic degradation of the peptides (Lai and Gallo 2009, Olsen and Potempa 2014, Bechinger and Gorr 2017), suppression of host AMP expression (Lai and Gallo 2009, Islam *et al*. 2001), modification of bacterial surface charge to reduce peptide binding (Malanovic and Lohner 2016, Bechinger and Gorr 2017), entrapment by cell surface proteins and polysaccharides (Bechinger and Gorr 2017), and active efflux of intracellular active AMPs (Alvarez-Ortega *et al*. 2013, Cole and Nizet 2016, Bechinger

and Gorr 2017). Despite these resistance mechanisms, AMPs remain fundamental components of eukaryotic innate immunity (Lai and Gallo 2009).

The long-term effectiveness of AMPs in nature is attributed to several factors. First, the evolution of resistance can impose substantial fitness costs on bacteria, particularly for AMPs that target and disrupt cell membranes, as alterations to membrane composition or cell wall architecture may compromise essential cellular integrity and function (Lai and Gallo 2009). In addition, many AMPs lack readily accessible recognition motifs for microbial proteases, limiting the capacity for selective degradation without simultaneously affecting essential microbial or host proteins. Importantly, organisms rarely rely on a single AMP in isolation, instead producing a diverse repertoire of peptides with distinct structures and complementary mechanisms of action (Lai and Gallo 2009, Me´nard *et al*. 2008). These peptides mixtures often act synergistically or additively. For example, in amphibian skin secretions, peptides such as magainins and dermaseptins cooperate functionally, with some permeabilizing bacterial membranes to facilitate the entry of others that target intracellular processes. Such cooperative interactions enhance antimicrobial efficacy while reducing the likelihood that resistance to a single peptide will permit microbial survival (Lai and Gallo 2009, Zasloff 2002, Zairi *et al*. 2009, Mookherjee *et al*. 2020). Although these features contribute to the sustained effectiveness of AMP-based responses in nature, resistance evolution may represent a more significant, albeit still comparatively limited consideration when single AMPs are applied in food preservation contexts. Particular attention should be directed toward capsule-forming bacteria, as extracellular polysaccharide capsules can act as a physical barrier that reduces AMP penetration and increases the likelihood of resistance development (Campos *et al*. 2004). To date, bacterial resistance to macins has not been investigated, representing an important knowledge gap and a priority for future research.

Environmental stability and prospective application of macins in food industry

One of the key considerations for the application of AMPs in food preservation is their stability under various environmental conditions encountered during food processing and storage (Singh *et al*. 2024). Several FDA-approved AMPs currently used as food preservatives have demonstrated sufficient stability to withstand environmental stressors commonly associated with industrial processing and long-term storage (Meena *et al*. 2021, Singh *et al*. 2024). Nevertheless, many AMPs remain susceptible to degradation under harsh physicochemical conditions (Shock 1992, Jung *et al*. 2012, Singh *et al*. 2024). Although their cationic and hydrophobic amino acid composition underpins membrane-targeting antimicrobial activity through electrostatic and hydrophobic interactions, these same properties also render them susceptible to degradation by food-derived proteases and peptidases, thereby reducing functional efficacy. Furthermore, environmental variables such as pH, temperature, and salinity can substantially influence AMPs stability and antimicrobial performance (He *et al*. 2023, Xu *et al*. 2023, Aoyama *et al*. 2025)

Among the currently characterised macins, mytimacin-4 demonstrated particularly high physicochemical resilience. Dong *et al*. (2024) reported that mytimacin-4 retained potent antibacterial activity across a broad temperature range (4°C–90°C), under highly acidic and alkaline conditions (pH 2 to 10), and in the presence of elevated NaCl concentrations (50–250 mmol l^{-1}). Importantly, the peptide also maintained antimicrobial activity following exposure to multiple proteolytic enzymes, including pepsin, papain, trypsin, and proteinase K. This resilience may be attributable to the environmental tolerance of the source organism, *Mytilus galloprovincialis*, an invasive intertidal species naturally exposed to fluctuating salinity and environmental stress. In addition, the cysteine-rich composition and highly constrained tertiary structure likely contributes to its structural robustness and resistance to denaturation or proteolytic degradation (Dong *et al*. 2024). Collectively, these findings suggest that mytimacin-4 may retain activity throughout food processing and storage, making it an attractive candidate for development as a natural food preservative.

In contrast, other macins, including HM1, neuromacin and theromacin appear more sensitive to elevated salt concentrations, with antimicrobial activity lost in the presence of 100 mmol l^{-1} NaCl (Jung *et al*. 2012). Such sensitivity may limit their applicability in salt-rich food matrices. These differences in physical properties may reflect the environmental conditions in which these peptides evolved, i.e. being isolated from freshwater organisms. Future studies should systematically evaluate the stability and antimicrobial efficacy of macins across a range of food matrices and processing conditions representative of real-world industrial applications, to identify peptides best suited for practical uses in food preservation systems.

Beyond intrinsic peptide stability, successful application in food systems will also depend on performance within complex food matrices, where fats, proteins and endogenous enzymes may reduce peptide bioavailability and antimicrobial activity (Kamdem and Tsopmo 2019). Delivery strategies such as encapsulation, edible coatings and incorporation into active packaging may help preserve peptide functionality and enhance improve applicability in food preservation (Aguilar-Toalá *et al*. 2022). In addition, considerations relating to toxicity, sensory impacts, production scalability, and regulatory approval will be critical for evaluating the translational potential of macins for industrial use. Together, these factors highlight both the considerable promise of macins and the key challenges that must be addressed before their practical implementation as food preservatives can be realized.

Conclusion

The macin family represents a distinctive yet comparatively underexplored group of AMPs, characterized by a conserved cysteine-rich structural framework coupled with substantial sequence diversity. Members of this family exhibit broad-spectrum antimicrobial activity, including potent activity against several major foodborne pathogens, while certain macins additionally possess immunomodulatory and tissue repair functions. In the context of escalating antimicrobial resistance and growing concerns surrounding the safety and sustainability of chemical preservatives, macins represent promising candidates for next-generation natural food preservation strategies. Nevertheless, significant knowledge gaps

remain regarding their mechanisms of action, evolutionary diversification, physicochemical stability, and performance within complex food systems. Addressing these challenges through further mechanistic, functional, and applied research will be essential to fully evaluate the translational potential of macins for sustainable food protection and preservation.

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Author contributions

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Supplementary material

Supplementary material is available at *Letters in Applied Microbiology Journal* online.

Conflicts of interest

Authors declare no conflict of interest.

Data availability

The data underlying this article are available in the article and in its online Supplementary material.

References

Aguilar-Toalá J, Quintanar-Guerrero D, Liceaga A *et al.* Encapsulation of bioactive peptides: a strategy to improve the stability, protect the nutraceutical bioactivity and support their food applications. *RSC Adv* 2022;**12**:6449–58. https://doi.org/10.1039/D1RA08590E

Al-Kharousi ZS, Guizani N, Al-Sadi AM *et al.* Hiding in fresh fruits and vegetables: opportunistic pathogens may cross geographical barriers. *Int J Microbiol* 2016;**2016**:4292417. https://doi.org/10.1155/2016/4292417

Alvarez-Ortega C, Olivares J, Martínez JL. RND multidrug efflux pumps: what are they good for? *Front Microbiol* 2013;**4**:7. https://doi.org/10.3389/fmicb.2013.00007

Aoyama K, Okai M, Ogawa N *et al.* A coral peptide with bactericidal activity against a global marine pathogen, *Vibrio coralliilyticus*. *iScience* 2025;**28**:113286. https://doi.org/10.1016/j.isci.2025.113286

Augustin R, Anton-Erxleben F, Jungnickel S *et al.* Activity of the novel peptide arminin against multiresistant human pathogens shows the considerable potential of phylogenetically ancient organisms as drug sources. *Antimicrob Agents Chemother* 2009;**53**:5245–50. https://doi.org/10.1128/AAC.00826-09

Bacon R, Sofos J, Scchmidt R *et al. Food safety handbook*. New York, USA:Wiley, 2003.

Bahar AA, Ren D. Antimicrobial peptides. *Pharmaceuticals* 2013;**6**:1543–75. https://doi.org/10.3390/ph6121543

Baik HS, Bearson S, Dunbar S *et al.* The acid tolerance response of *Salmonella typhimurium* provides protection against organic acids. *Microbiology* 1996;**142**:3195–200. https://doi.org/10.1099/13500872-142-11-3195

Bechinger B, Gorr S-U. Antimicrobial peptides: mechanisms of action and resistance. *J Dent Res* 2017;**96**:254–60. https://doi.org/10.1177/0022034516679973

Bin Hafeez A, Jiang X, Bergen PJ *et al.* Antimicrobial peptides: an update on classifications and databases. *Int J Mol Sci* 2021;**22**:11691.

Bintsis T. Foodborne pathogens. *AIMS Microbiol* 2017;**3**:529. https://doi.org/10.3934/microbiol.2017.3.529

Boidin-Wichlacz C, Vergote D, Slomianny C *et al.* Morphological and functional characterization of leech circulating blood cells: role in immunity and neural repair. *Cell Mol Life Sci* 2012;**69**:1717–31. https://doi.org/10.1007/s00018-011-0897-x

Bosch TC, Augustin R, Anton-Erxleben F *et al.* Uncovering the evolutionary history of innate immunity: the simple metazoan *Hydra* uses epithelial cells for host defence. *Dev Comp Immunol* 2009;**33**:559–69. https://doi.org/10.1016/j.dci.2008.10.004

Bracey D, Holyoak C, Coote PJ. Comparison of the inhibitory effect of sorbic acid and amphotericin B on *Saccharomyces cerevisiae*: is growth inhibition dependent on reduced intracellular pH? *J Appl Microbiol* 1998;**85**:1056–66. https://doi.org/10.1111/j.1365-2672.1998.tb05271.x

Brötz H, Bierbaum G, Reynolds PE *et al.* The lantibiotic mersacidin inhibits peptidoglycan biosynthesis at the level of transglycosylation. *Eur J Biochem* 1997;**246**:193–9.

Brul S, Coote P. Preservative agents in foods: mode of action and microbial resistance mechanisms. *Int J Food Microbiol* 1999;**50**:1–17. https://doi.org/10.1016/S0168-1605(99)00072-0

Campos MA, Vargas MA, Regueiro V *et al.* Capsule polysaccharide mediates bacterial resistance to antimicrobial peptides. *Infect Immun* 2004;**72**:7107–14. https://doi.org/10.1128/IAI.72.12.7107-7114.2004

Ceruso M, Clement JA, Todd MJ *et al.* The inhibitory effect of plant extracts on growth of the foodborne pathogen, *Listeria monocytogenes*. *J Antibiot* 2020;**9**:319. https://doi.org/10.3390/antibiotics9060319

Cole JN, Nizet V. Bacterial evasion of host antimicrobial peptide defenses. *Virulence Mechanisms of Bacterial Pathogens* 2016:413–43. https://doi.org/10.1128/9781555819286

Corbalán N, Quiroga M, Masias E *et al.* Antimicrobial activity of MccJ25 (G12Y) against Gram-negative foodborne pathogens *in vitro* and in food models. *Int J Food Microbiol* 2021;**352**:109267. https://doi.org/10.1016/j.ijfoodmicro.2021.109267

da Costa RJ, Voloski FL, Mondadori RG *et al.* Preservation of meat products with bacteriocins produced by lactic acid bacteria isolated from meat. *J Food Qual* 2019;**2019**:4726510.

Dell'Olmo E, Gaglione R, Sabbah M *et al.* Host defense peptides identified in human apolipoprotein B as novel food bio-

preservatives and active coating components. *Food Microbiol* 2021;**99**:103804.

Demir R, Sarıtaş S, Bechelany M *et al.* Lactoferrin: properties and potential uses in the food industry. *Int J Mol Sci* 2025;**26**:1404. https://doi.org/10.3390/ijms26041404

De Stefano F, Rinaldi R, Derin E *et al.* Secondary products and bioactive compounds of *Hermetia illucens*: extraction, chemical properties, and potential application of antimicrobial peptides. In *The Black Soldier Fly (Hermetia illucens)*. 2026, 221–56.

Ding A, Shi H, Guo Q *et al.* Gene cloning and expression of a partial sequence of Hirudomacin, an antimicrobial protein that is increased in leech (*Hirudo nipponica* Whitman) after a blood meal. *Comp Biochem Physiol Part B Biochem Mol Biol* 2019;**231**:75–86. https://doi.org/10.1016/j.cbpb.2019.02.005

Dong B, Wang Y, Cui G *et al. In vitro* antimicrobial activity of the novel antimicrobial peptide mytimacin-4 and its influence on the microbial community and quality of pork during refrigerated storage. *Food Control* 2024;**163**:110486. https://doi.org/10.1016/j.foodcont.2024.110486

Dong B, Yu C, Lin Y *et al.* Antimicrobial property of *Pichia pastoris*-derived natto peptide against foodborne bacteria and its preservative potential to maintain pork quality during refrigerated storage. *Food Sci Nutr* 2022;**10**:914–25. https://doi.org/10.1002/fsn3.2722

Du Y, Shi H, Guo Q *et al.* Hirudomacin: a protein with dual effects of direct bacterial inhibition and regulation of innate immunity. *Appl Environ Microb* 2023;**89**:e00527–23. https://doi.org/10.1128/aem.00527-23

Egessa R. Antimicrobial peptides from freshwater invertebrate species: potential for future applications. *Mol Biol Rep* 2022;**49**:9797–811. https://doi.org/10.1007/s11033-022-07483-1

Elbehiry A, Marzouk E, Abalkhail A *et al.* Microbial food safety and antimicrobial resistance in foods: a dual threat to public health. *Microorganisms* 2025;**13**:1592. https://doi.org/10.3390/microorganisms13071592

Erdem Büyükkiraz M, Kesmen Z. Antimicrobial peptides (AMPs): a promising class of antimicrobial compounds. *J Appl Microbiol* 2022;**132**:1573–96. https://doi.org/10.1111/jam.15314

Espitia P, Otoni C, Soares N. Pediocin applications in antimicrobial food packaging systems. In *Antimicrobial food packaging*. 2025:623–34.

Field D, Fernandez de Ullivarri M, Ross RP *et al.* After a century of nisin research-where are we now? *FEMS Microbiol Rev* 2023;**47**:fuad023. https://doi.org/10.1093/femsre/fuad023

Freese E, Sheu CW, Galliers E. Function of lipophilic acids as antimicrobial food additives. *Nature* 1973;**241**:321–5. https://doi.org/10.1038/241321a0

Gallo RL, Murakami M, Ohtake T *et al.* Biology and clinical relevance of naturally occurring antimicrobial peptides. *Allergy Clin Immunol* 2002;**110**:823–31. https://doi.org/10.1067/mai.2002.129801

García-Penas I, Campillo R, Berdejo D *et al.* Evolution of *Salmonella Typhimurium* under antibiotics from distinct classes reveals variant-dependent cross-protection against food preservation treatments. *Food Microbiol* 2026;**139**:105138. https://doi.org/10.1016/j.fm.2026.105138

Gasteiger E, Hoogland C, Gattiker A *et al.* Protein identification and analysis tools on the ExPASy server. In *The proteomics protocols handbook*. Springer, 2005,571–607. https://doi.org/10.1385/1592598900

Gerdol M, De Moro G, Manfrin C *et al.* Big defensins and mytimacins, new AMP families of the Mediterranean mussel *Mytilus galloprovincialis*. *Dev Comp Immunol* 2012;**36**:390–9. https://doi.org/10.1016/j.dci.2011.08.003

Gerdol M, Venier P. An updated molecular basis for mussel immunity. *Fish Shellfish Immunol* 2015;**46**:17–38. https://doi.org/10.1016/j.fsi.2015.02.013

Hanchi H, Mottawea W, Sebei K *et al.* The genus *Enterococcus*: between probiotic potential and safety concerns—an update. *Front Microbiol* 2018;**9**:1791. https://doi.org/10.3389/fmicb.2018.01791

Hasenböhler A, Javaux G, de la Garanderie MP *et al.* Intake of food additive preservatives and incidence of cancer: results from the NutriNet-Santé prospective cohort. *BMJ* 2026;**392**:e084917.

He S, Yang Z, Li X *et al.* Boosting stability and therapeutic potential of proteolysis-resistant antimicrobial peptides by end-tagging β-naphthylalanine. *Acta Biomater* 2023;**164**:175–94. https://doi.org/10.1016/j.actbio.2023.04.030

Hiraki J, Ichikawa T, Ninomiya S-iet al. Use of ADME studies to confirm the safety of ε-polylysine as a preservative in food. *Regul Toxicol Pharmacol* 2003;**37**:328–40. https://doi.org/10.1016/S0273-2300(03)00029-1

Hu H, Shao Y, Yang L *et al.* Molecular characterization and immunological functions of the antimicrobial peptide theromacin from razor clam *Sinonovacula constricta*. *Int J Biol Macromol* 2025;**308**:142312. https://doi.org/10.1016/j.ijbiomac.2025.142312

Hung C-W, Jung S, Grötzinger J *et al.* Determination of disulfide linkages in antimicrobial peptides of the macin family by combination of top-down and bottom-up proteomics. *J Proteomics* 2014;**103**:216–26. https://doi.org/10.1016/j.jprot.2014.04.001

Ilyas H, Kim J, Lee D *et al.* Structural insights into the combinatorial effects of antimicrobial peptides reveal a role of aromatic–aromatic interactions in antibacterial synergism. *J Biol Chem* 2019;**294**:14615–33. https://doi.org/10.1074/jbc.RA119.009955

Islam D, Bandholtz L, Nilsson J *et al.* Downregulation of bactericidal peptides in enteric infections: a novel immune escape mechanism with bacterial DNA as a potential regulator. *Nat Med* 2001;**7**:180–5. https://doi.org/10.1038/84627

Jenssen H, Hamill P, Hancock RE. Peptide antimicrobial agents. *Clin Microbiol Rev* 2006;**19**:491–511. https://doi.org/10.1128/CMR.00056-05

Jiao C, Ruan J, Sun W *et al.* Molecular characterization, expression and antibacterial function of a macin, HdMac, from *Haliotis discus hannai*. *J Invertebr Pathol* 2024;**204**:108113. https://doi.org/10.1016/j.jip.2024.108113

Joo M-S, Choi K-M, Cho D-H *et al.* The molecular characterization, expression analysis and antimicrobial activity of theromacin from Asian polychaeta (*Perinereis linea*). *Dev Comp Immunol* 2020;**112**:103773. https://doi.org/10.1016/j.dci.2020.103773

Jung S, Dingley AJ, Augustin R *et al.* Hydramacin-1, structure and antibacterial activity of a protein from the basal metazoan *Hydra*. *J Biol Chem* 2009;**284**:1896–905. https://doi.org/10.1074/jbc.M804713200

Jung S, Mysliwy J, Spudy B *et al.* Human β-defensin 2 and β-defensin 3 chimeric peptides reveal the structural basis of the pathogen specificity of their parent molecules. *Antimicrob*

Agents Chemother 2011;**55**:954–60. https://doi.org/10.1128/AAC.00872-10

Jung S, Sönnichsen FD, Hung C-W *et al.* Macin family of antimicrobial proteins combines antimicrobial and nerve repair activities. *J Biol Chem* 2012;**287**:14246–58. https://doi.org/10.1074/jbc.M111.336495

Kamdem JP, Tsopmo A. Reactivity of peptides within the food matrix. *J Food Biochem* 2019;**43**:e12489. https://doi.org/10.1111/jfbc.12489

Kanatt SR, Chander R, Sharma A. Chitosan and mint mixture: a new preservative for meat and meat products. *Food Chem* 2008;**107**:845–52. https://doi.org/10.1016/j.foodchem.2007.08.088

Kasimin ME, Shamsuddin S, Molujin AM *et al.* Enterocin: promising biopreservative produced by *Enterococcus* sp. *Microorganisms* 2022;**10**:684. https://doi.org/10.3390/microorganisms10040684

Kawsar MA, Zhao C, Mao F *et al.* Unlocking antimicrobial peptides from marine invertebrates: a comprehensive review of antimicrobial discovery. *Antibiotics* 2025;**14**:924. https://doi.org/10.3390/antibiotics14090924

Kumar R, Ali SA, Singh SK *et al.* Antimicrobial peptides in farm animals: an updated review on its diversity, function, modes of action and therapeutic prospects. *Vet Sci* 2020;**7**:206. https://doi.org/10.1016/j.rvsc.2020.05.003

Lai Y, Gallo RL. AMPed up immunity: how antimicrobial peptides have multiple roles in immune defense. *Trends Immunol* 2009;**30**:131–41. https://doi.org/10.1016/j.it.2008.12.003

Lee J, Sung J-M, Cho HJ *et al.* Natural extracts as inhibitors of microorganisms and lipid oxidation in emulsion sausage during storage. *Food Sci Anim Resour* 2021;**41**:1060. https://doi.org/10.5851/kosfa.2021.e58

Liu J, Hou Y, Zhao L *et al.* Antimicrobial resistance and the genomic epidemiology of multidrug-resistant *Salmonella enterica* serovar Enteritidis ST11 in China. *Front Biosci—Landmark* 2024;**29**:112. https://doi.org/10.31083/j.fbl2903112

Lv J, Zhao J, Yang D *et al.* Tissue distribution and functional characterization of mytimacin-4 in *Mytilus galloprovincialis*. *J Invertebr Pathol* 2019;**166**:107215. https://doi.org/10.1016/j.jip.2019.107215

Ma C, Deng X, Ke C *et al.* Epidemiology and etiology characteristics of foodborne outbreaks caused by *Vibrio parahaemolyticus* during 2008–2010 in Guangdong province, China. *Foodborne Pathog Dis* 2014;**11**:21–9. https://doi.org/10.1089/fpd.2013.1522

Malanovic N, Lohner K. Gram-positive bacterial cell envelopes: the impact on the activity of antimicrobial peptides. *Biochim Biophys Acta—Biomembranes* 2016;**1858**:936–46. https://doi.org/10.1016/j.bbamem.2015.11.004

Manyi-Loh C, Mamphweli S, Meyer E *et al.* Antibiotic use in agriculture and its consequential resistance in environmental sources: potential public health implications. *Molecules* 2018;**23**:795. https://doi.org/10.3390/molecules23040795

Meena M, Prajapati P, Ravichandran C *et al.* Natamycin: a natural preservative for food applications—a review. *Food Sci Biotechnol* 2021;**30**:1481–96. https://doi.org/10.1007/s10068-021-00981-1

Me´nard S, Fo¨rster V, Lotz M *et al.* Developmental switch of intestinal antimicrobial peptide expression. *J Exp Med* 2008;**205**:183–93. https://doi.org/10.1084/jem.20071022

Meng S, Xu H, Wang F. Research advances of antimicrobial peptides and applications in food industry and agriculture. *Curr Protein Pept Sci* 2010;**11**:264–73. https://doi.org/10.2174/138920310791233369

Michalek M, Vincent B, Podschun R *et al.* Hydramacin-1 in action: scrutinizing the barnacle model. *Antimicrob Agents Chemother* 2013;**57**:2955–66. https://doi.org/10.1128/AAC.02498-12

Mohammadzadeh-Aghdash H, Akbari N, Esazadeh K *et al.* Molecular and technical aspects on the interaction of serum albumin with multifunctional food preservatives. *Food Chem* 2019;**293**:491–8. https://doi.org/10.1016/j.foodchem.2019.04.119

Mookherjee N, Anderson MA, Haagsman HP *et al.* Antimicrobial host defence peptides: functions and clinical potential. *Nat Rev Drug Discov* 2020;**19**:311–32. https://doi.org/10.1038/s41573-019-0058-8

Moretta A, Scieuzo C, Petrone AM *et al.* Antimicrobial peptides: a new hope in biomedical and pharmaceutical fields. *Front Cell Infect Microbiol* 2021;**11**:668632. https://doi.org/10.3389/fcimb.2021.668632

Murray CJ, Ikuta KS, Sharara F *et al.* Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* 2022;**399**:629–55. https://doi.org/10.1016/S0140-6736(21)02724-0

Nazir A, Nazir A, Zuhair V *et al.* The global challenge of antimicrobial resistance: mechanisms, case studies, and mitigation approaches. *Health Sci Rep* 2025;**8**:e71077. https://doi.org/10.1002/hsr2.71077

Neonakis IK, Spandidos DA, Petinaki E. Confronting multidrug-resistant *Acinetobacter baumannii*: a review. *Int J Antimicrob Agents* 2011;**37**:102–9. https://doi.org/10.1016/j.ijantimicag.2010.10.014

Nhung NT, Van NTB, Van Cuong N *et al.* Antimicrobial residues and resistance against critically important antimicrobials in non-typhoidal *Salmonella* from meat sold at wet markets and supermarkets in Vietnam. *Int J Food Microbiol* 2018;**266**:301–9. https://doi.org/10.1016/j.ijfoodmicro.2017.12.015

Nizet V. Antimicrobial peptide resistance mechanisms of human bacterial pathogens. *Curr Iss Mol Biol* 2006;**8**:11–26.

Olsen I, Potempa J. Strategies for the inhibition of gingipains for the potential treatment of periodontitis and associated systemic diseases. *J Oral Microbiol* 2014;**6**:24800. https://doi.org/10.3402/jom.v6.24800

Otero-Gonzáiez AJ, Magalhaes BS, Garcia-Villarino M *et al.* Antimicrobial peptides from marine invertebrates as a new frontier for microbial infection control. *FASEB J* 2010;**24**:1320–34. https://doi.org/10.1096/fj.09-143388

Pasupuleti M, Schmidtchen A, Malmsten M. Antimicrobial peptides: key components of the innate immune system. *Crit Rev Biotechnol* 2012;**32**:143–71. https://doi.org/10.3109/07388551.2011.594423

Perri R, Kolvenbach BA, Corvini PF. Subsistence and complexity of antimicrobial resistance on a community-wide level. *Environ Microbiol* 2020;**22**:2463–8. https://doi.org/10.1111/1462-2920.15018

Piper PW. Resistance of yeasts to weak organic acid food preservatives. In *Advances in applied microbiology*. Elsevier, 2011,97–113.

Purgatorio C, Serio A, Chaves-López C *et al.* An overview of the natural antimicrobial alternatives for sheep meat preservation.

Compr Rev Food Sci Food Saf 2022;**21**:4210–50. https://doi.org/10.1111/1541-4337.13004

Raheem N, Straus SK. Mechanisms of action for antimicrobial peptides with antibacterial and antibiofilm functions. *Front Microbiol* 2019;**10**:2866. https://doi.org/10.3389/fmicb.2019.02866

Recoules C, Touvier M, Pierre F *et al.* Evaluation of the toxic effects of food additives, alone or in mixture, in four human cell models. *Food Chem Toxicol* 2025;**196**:115198. https://doi.org/10.1016/j.fct.2024.115198

Santos-Júnior CD, Torres MD, Duan Y *et al.* Discovery of antimicrobial peptides in the global microbiome with machine learning. *Cell* 2024;**187**:3761–78.e16. https://doi.org/10.1016/j.cell.2024.05.013

Scallan E, Hoekstra RM, Angulo FJ *et al.* Foodborne illness acquired in the United States—major pathogens. *Emerg Infect Dis* 2011;**17**:7. https://doi.org/10.3201/eid1701.P11101

Schikorski D, Cuvillier-Hot V, Leippe M *et al.* Microbial challenge promotes the regenerative process of the injured central nervous system of the medicinal leech by inducing the synthesis of antimicrobial peptides in neurons and microglia. *J Immunol* 2008;**181**:1083–95. https://doi.org/10.4049/jimmunol.181.2.1083

Schwab U, Gilligan P, Jaynes J *et al.* In vitro activities of designed antimicrobial peptides against multidrug-resistant cystic fibrosis pathogens. *Antimicrob Agents Chemother* 1999;**43**:1435–40. https://doi.org/10.1128/AAC.43.6.1435

Shock EL. Stability of peptides in high-temperature aqueous solutions. *Geochim Cosmochim Acta* 1992;**56**:3481–91. https://doi.org/10.1016/0016-7037(92)90392-V

Singh S, Jha B, Tiwari P *et al.* Recent approaches in the application of antimicrobial peptides in food preservation. *World J Microbiol Biotechnol* 2024;**40**:315. https://doi.org/10.1007/s11274-024-04126-4

Tang B, Chang J, Luo Y *et al.* Prevalence and characteristics of the mcr-1 gene in retail meat samples in Zhejiang Province, China. *J Microbiol* 2022;**60**:610–9. https://doi.org/10.1007/s12275-022-1597-y

Tasiemski A, Vandenbulcke F, Mitta G *et al.* Molecular characterization of two novel antibacterial peptides inducible upon bacterial challenge in an annelid, the leech Theromyzon tessulatum. *J Biol Chem* 2004;**279**:30973–82. https://doi.org/10.1074/jbc.M312156200

Tasiemski A. Antimicrobial peptides in annelids. *Invertebr Surviv J* 2008;**5**:75–82.

Triunfo M, Guarnieri A, Ianniciello D *et al.* Secondary products and bioactive compounds of Hermetia illucens: extraction, chemical properties, and potential application of chitin and chitosan. In *The Black Soldier Fly (Hermetia illucens)*. Elsevier, 2026,155–88.

Viazis S, Lindsay M, Cripe J *et al.* An overview of multistate outbreak investigations of *salmonella* infections linked to fish and fishery products, US–2012–2021. *J Food Prot* 2025;**88**:100566. https://doi.org/10.1016/j.jfp.2025.100566

Vojkovská H, Myšková P, Gelbíčová T *et al.* Occurrence and characterization of food-borne pathogens isolated from fruit, vegetables and sprouts retailed in the Czech Republic. *Food Microbiol* 2017;**63**:147–52. https://doi.org/10.1016/j.fm.2016.11.012

WHO GS. Joint FAO/WHO Expert Meeting in collaboration with OIE on Foodborne Antimicrobial Resistance: role of the Environment, Crops and Biocides. 2019.

Wilmes M, Cammue BP, Sahl H-G *et al.* Antibiotic activities of host defense peptides: more to it than lipid bilayer perturbation. *Nat Prod Rep* 2011;**28**:1350–8. https://doi.org/10.1039/c1np00022e

Woo S-H, Sung J-M, Park H *et al.* Inhibitory effect of natural extract mixtures on microbial growth and lipid oxidation of sausages during storage. *J Anim Sci Technol* 2023;**65**:225. https://doi.org/10.5187/jast.2022.e92

Xie Z, Yao T, Ye L *et al.* Molecular characterization and expression analysis of an antimicrobial peptide, mytimacin-6, in the small abalone, *Haliotis diversicolor*. *Isr J Aquac - Bamidgeh* 2021;**73**:1–11.

Xu S, Tan P, Tang Q *et al.* Enhancing the stability of antimicrobial peptides: from design strategies to applications. *Chem Eng J* 2023;**475**:145923. https://doi.org/10.1016/j.cej.2023.145923

Xue R, Han Y, Li F *et al.* Identification, antibacterial activities and action mode of two macins from manila clam Venerupis philippinarum. *Fish Shellfish Immunol* 2021;**118**:411–20. https://doi.org/10.1016/j.fsi.2021.09.031

Yang D, Han Y, Chen L *et al.* A macin identified from *Venerupis philippinarum*: investigation on antibacterial activities and action mode. *Fish Shellfish Immunol* 2019;**92**:897–904. https://doi.org/10.1016/j.fsi.2019.07.031

Yang H, Xiang K, Li Y *et al.* Novel AIE luminogen containing axially chiral BINOL and tetraphenylsilole. *J Organomet Chem* 2016;**801**:96–100. https://doi.org/10.1016/j.jorganchem.2015.10.017

Younes M, Aggett P, Aguilar F *et al.* Safety of nisin (E 234) as a food additive in the light of new toxicological data and the proposed extension of use. *EFSA J* 2017;**15**:e05063.

Yu Y, Tang L, Xiao M *et al.* Genetic Variation and Gene Expression of the Antimicrobial Peptide Macins in Asian Buffalo Leech (*Hirudinaria manillensis*). *J Biol* 2025;**14**:517. https://doi.org/10.3390/biology14050517

Zairi A, Tangy F, Bouassida K *et al.* Dermaseptins and Magainins: antimicrobial Peptides from Frogs′ Skin—New Sources for a Promising Spermicides Microbicides—a Mini Review. *BioMed Res Int* 2009;**2009**:452567. https://doi.org/10.1155/2009/452567

Zasloff M. Antimicrobial peptides of multicellular organisms. *Nature* 2002;**415**:389–95. https://doi.org/10.1038/415389a

Zhang Q-Y, Yan Z-B, Meng Y-M *et al.* Antimicrobial peptides: mechanism of action, activity and clinical potential. *Mil Med Res* 2021;**8**:48.

Zhang W, Huang M, Shi H *et al.* Antibacterial mechanism and immunomodulatory function of a new Macin family peptide from *Pinctada fucata*. *Aquaculture* 2025:743331.

Zheng Z, Ye L, Xu Y *et al.* Dynamics of antimicrobial resistance and genomic characteristics of foodborne *Vibrio* spp. In **SOUTHERN CHINA** (2013–2022). *J Hazard Mater* 2024;**479**:135672. https://doi.org/10.1016/j.jhazmat.2024.135672

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