Pertanika J. Sci. & Technol. 32 (6): 2847 - 2872 (2024)

SCIENCE & TECHNOLOGY

Journal homepage: http://www.pertanika.upm.edu.my/

Review Article

A Systematic Review of Aquatic Organism Antimicrobial Peptides

Li Ting Lee[1], Arnold Ang[1], Ibrahim Mahmood[2], Ahmed AbdulKareem Najm[3], Adura Mohd Adnan[1], Shazrul Fazry[3,4] and Douglas Law[1,5]*

[1]*Faculty of Health and Life Sciences, Inti International University, Persiaran Perdana BBN Putra Nilai, 71800, Nilai, Negeri Sembilan, Malaysia*
[2]*Al Rafidain University College, 9c74+prq, Baghdad, Baghdad Governorate, 46036, Iraq*
[3]*Department of Food Sciences, Faculty of Science and Technology, Universiti Kebangsaan Malaysia, 43600, Bangi, Selangor Darul Ehsan, Malaysia*
[4]*Chini Lake Research Centre, Faculty of Science and Technology, Universiti Kebangsaan Malaysia, 43600, Bangi, Selangor Darul Ehsan, Malaysia*
[5]*ENIAC, Centro Universitario de Excelencia. R. Força Pública, 89, Centro Guarulhos-SP, 07012-030, Brazil*

ABSTRACT

Antimicrobial peptides (AMPs), sourced from various organisms, including aquatic life, are promising alternatives to combat antibiotic resistance. Their investigation is essential amid global antibiotic resistance concerns. The invaluable impact of antibiotics on human health, having saved numerous lives, is currently at risk. The growing global incidence of antibiotic-resistant bacteria poses a serious challenge to their ability to effectively treat various illnesses. This situation demands immediate attention and the exploration of alternative medical solutions. One of the most promising alternatives to antibiotics is antimicrobial peptides (AMPs), which can treat bacterial infections, particularly those brought by multi-drug-resistant pathogens. With a particular focus on their antimicrobial properties, this systematic review aims to evaluate and classify recent AMPs isolated from aquatic organisms. This review advances knowledge of these aquatic life-derived AMPs' potential as alternatives to conventional antibiotics by examining their unique antibacterial characteristics and modes of action. A systematic review of articles published in English between 2014 and 2024 was carried out in the Science Direct, PubMed NCBI and Google Scholar

ARTICLE INFO

Article history:
Received: 10 December 2023
Accepted: 10 July 2024
Published: 25 October 2024

DOI: https://doi.org/10.47836/pjst.32.6.23

E-mail addresses:
i20018708@student.newinti.edu.my (Li Ting Lee)
i19017161@student.newinti.edu.my (Arnold Ang)
ibrahim_m_mahdy@yahoo.com (Ibrahim Mahmood)
ahmad_aljemeely@yahoo.com (Ahmed AbdulKareem Najm)
adura.mohdadnan@newinti.edu.my (Adura Mohd Adnan)
shazrul@ukm.edu.my (Shazrul Fazry)
douglas.law@gmail.com (Douglas Law)
* Corresponding author

ISSN: 0128-7680
e-ISSN: 2231-8526

databases using keywords and inclusion and exclusion criteria. A total of 33 potential AMPs isolated from aquatic organisms had been reported, and 21 of the AMPs were reported to have functional antimicrobial activities. Continuous research and study of natural substances, particularly AMPs, remain critical in pursuing alternatives to conventional antibiotics for effective treatments in combating antibiotic resistance. Therefore, ongoing research holds significant importance in identifying and harnessing the potential of AMPs for future medical applications.

Keywords: Antibiotics, antimicrobial peptides, aquatic life, human health, microbes

INTRODUCTION

The aquatic environment makes up more than 70% of the planet's surface. It is a habitat for such a variety of chemicals and serves as a vast supply of possible therapeutic agents. Although it is well known that the aquatic environment is one of the richest sources of antimicrobial peptides, little is known about this ecosystem. Fish, mollusks and even sponges that live in the ocean produce a variety of AMPs with various structures and purposes. These peptides frequently have strong antibacterial properties on viruses, fungi, and even bacteria (Semreen et al., 2018; Pelle et al., 2020; Peng et al., 2012; Vitali, 2018).

Antibiotics are not only often used but also misused worldwide. The effectiveness of antibiotics, which have revolutionized medicine and saved millions of lives, used in treatment for certain kinds of disease, is in jeopardy due to the increasing rise of resistant bacteria worldwide. After the first batch of patients were treated using an antibiotic for several decades, bacterial infections have again become a danger in the world (Subramaniam et al., 2020). The bacterial microbiome that typically resides in the gut is crucial to health. In areas like the vagina and gut, antibiotics frequently kill beneficial flora and result in opportunistic infections. 50% of antibiotic prescriptions for illnesses are thought to be unneeded (Sepulveda & Wilson, 2019). Studies have indicated that between 30% and 50% of the time, treatment indications, agent selections, or antibiotic medication duration need to be more accurate.

One of the most promising alternatives to antibiotics is antimicrobial peptides (AMPs), which can treat bacterial infections, particularly those brought on by multidrug-resistant pathogens (Rima et al., 2021; Xuan et al., 2023). AMPs are defined as a class of small peptides ranging from 10 to 50 amino acids, which play an important part in the immune systems of various organisms (Huan et al., 2020). These bioactive compounds pose the first line of defense for the host organism against bacteria, viruses, and fungi (Moretta et al., 2021). When used against several kinds of bacteria, yeasts, fungi, viruses, and parasites, natural AMPs have robust and broad-spectrum activity, exhibiting bacteriostatic, microbicidal, and cytolytic capabilities (Moretta et al., 2021). They have broad-spectrum activity and can kill Gram-positive and Gram-negative bacteria, which is particularly useful given the increasing prevalence of antibiotic-resistant bacteria (Zasloff, 2002). Besides their antibacterial properties, these AMPs have also exhibited other properties such as anticancer, anti-fungal as well as antiviral properties, which genuinely shows their diversity and versatility in becoming the future of alternative medication to treat illnesses and diseases (Huan et al., 2020; Uddin et al., 2021).

MATERIALS AND METHODS

This study aims to systematically review recent research on AMPs derived from aquatic organisms, emphasizing their antimicrobial activities and mode of action. The preferred reporting items for systematic reviews and meta-analysis (PRISMA) method will be applied to this study. From this systematic review, we aim to delve into the question: Are naturally occurring antimicrobial peptides derived from fish viable against human pathogenic bacteria? Could modifications on these peptides lead to better antibacterial properties than naturally occurring ones?

Search Strategy

Google Scholar, Science Direct, Frontiers and PubMed NCBI are the four electronic databases used and searched in July 2023. Boolean operators ('AND,' 'OR') were used in the advanced search to combine words or phrases. The following MeSH (Medical Subject Headings) keywords or phrases were used: "antimicrobial peptides" AND "aquatic organism" OR "fish" OR "marine life" AND "microbes" AND "antibiotic resistance". Truncations, brackets, and quotation marks were used for an advanced search whenever possible.

Eligibility Criteria

A series of eligibility criteria were determined by the authors to ensure the quality of the studies reviewed: (1) the papers must be either a research paper or a review paper (systematic review, literature review, scope review) curated and published in the English language between 2014 and 2023, (2) the research scope of the papers should involve antimicrobial peptides derived from aquatic organism which show antibacterial properties. Studies that included synthesized peptides or peptides with no antibacterial properties and derived from sources other than marine life were excluded, and (3) the design and quality of the studies will also be appraised. Any studies that have failed the quality appraisal will be excluded from this review.

Search Outcomes

Figure 1 shows the PRISMA flow diagram. Figure 1 shows that 952 studies were found using the four electronic databases. There were still 952 studies remaining after excluding

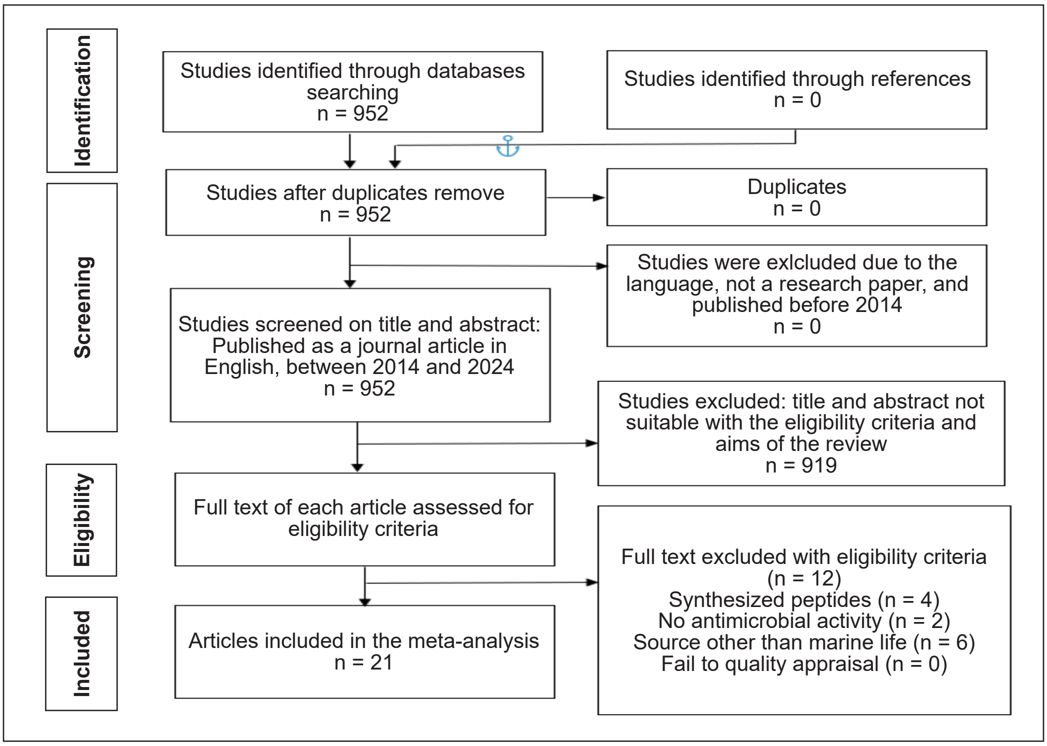

Figure 1. PRISMA flow diagram of antimicrobial peptides derived from aquatic organisms on microbes

the duplicate research and non-scientific manuscripts during the study period between 2014-2024 and excluding languages other than English.

Data Extraction and Quality Appraisal

The authors used a multiple-assessment approach to identify, screen, and choose studies using PRISMA guidelines with frequent iterations of the screening, analysis, and synthesized processes (Moher et al., 2009). To assess the consistency and dependability of studies, the authors also carried out the quality appraisal approach used in the current study (Moher et al., 2009; Walsh & Downe, 2006). The articles were evaluated using Russell and Gregory's (2003) Guide for Evaluating Qualitative Research Studies. The observational and clinical studies were assessed using the Evidence-based Practice Centers (EPCs), the Scientific Resource Centre, and the Agency for Healthcare Research and Quality's (AHRQ) Methods Guide for Medical Test Reviews, which made the evaluation methods consistent (Chang et al., 2012; Munn et al., 2015). According to Walsh and Downe (2006), articles were labeled as embodying high bias or risk if they met less than 70% of the assessment criteria. A summary of the included articles was presented in Table 1, which shows the reference and year of study, study objective, study methodology, biological sample used, and main findings.

Table 1
Summary of the reported aquatic organism's antimicrobial peptide from the reviewed studies

Study Objective	Methods	Biological Sample	Main Findings	Activity	References	Effects
To identify and analyze the antimicrobial peptide dromidin, which was extracted from the hemolymph of the sea crab Dromia dehaani, and to investigate its antibacterial properties for potential new medicinal uses.	Experimental method using ESI-MS analysis	Species: Hemolymph of marine crab *Dromia dehaani*	This study used the hemolymph of the sea crab *Dromia dehaani* to isolate and characterize the new antibacterial peptide known as Dromidin. Researchers established the existence of Dromidin utilizing various analytical methods, including ESI-MS analysis, which showed a molecular weight of 513.0 Da. These results support its importance as an antibacterial agent and advance our knowledge of bioactive marine chemicals with potential use in pathogen defense.	Antimi-crobial Activity	Anbuchezian et al., 2018	Confirmed antibacterial activity against bacterial pathogens
To produce recombinant antimicrobial proteins from the marine diatom Phaeodactylum tricornutum (S-thanatin and bovine lactoferricin) and test their efficiency against gram-negative bacteria, particularly E. cloacae and V. natriegens.	Experimental method using antimicrobial activity assays and Western Blot	Species: Lysate of the marine diatom *Phaeodactylum tricornutum*	*Phaeodactylum tricornutum*, a sea diatom genetically altered to generate the powerful antimicrobial proteins S-thanatin and bLFcin, offers a remedy for antibiotic resistance. These microalgae successfully defeat gram-negative bacteria like *V. natriegens* and *E. cloac*ae. The strain that expressed bLFcin had the most efficacy, promising a natural antibiotic substitute for bacterial infections and antimicrobial resistance.	Antimi-crobial Activity	Baiden et al., 2023	Confirmed antibacterial activity towards gram-negative bacteria
Identify and assess antimicrobial peptides (AMPs) in rockfish Sebastiscus marmoratus for potential therapeutic application in aquacumlture.	Analysis of liver transcriptome and real-time quantitative PCR (RT-qPCR) for AMP identification and expression profiling	*Sebastiscus marmoratus*	6 AMPs were identified, with LEAP-2 and Moronecidin showing broad-spectrum antimicrobial activity against aquatic pathogens without cytotoxicity, suggesting their potential as therapeutic agents in aquaculture to combat pathogenic infections.	Antimi-crobial Activity	Bo et al., 2019	Confirmed antibacterial activity against aquatic pathogens

Table 1 *(continue)*

Study Objective	Methods	Biological Sample	Main Findings	Activity	References	Effects
To investigate the interaction between bacteria and a newly created mutant peptide termed Cnd-m3a produced from the Antarctic icefish Chionodraco hamatus, as well as its potential as a treatment for human diseases.	The experimental method involves isolation and identification using transmission electron microscopy (TEM), fluorescent probe assays, and in vitro assays.	Species: Antarctic icefish *Chionodraco hamatus*, from which the initial Cnd peptide and its mutant derivative Cnd-m3a were isolated	The effective creation of the mutant peptide Cnd-m3a has increased antibacterial action against human infections and improved selectivity against prokaryotic cells. The study also emphasizes how Cnd-m3a interacts with Psychrobacter sp. (TAD1), an Antarctic bacterium, and its capacity to pierce the outer membrane of bacteria like E. coli and Psychrobacter sp. Furthermore, Cnd-m3a demonstrated limited cytotoxic and hemolytic effects on human cells but strong antibacterial activity against a subset of Gram-negative human pathogens, highlighting its potential as a platform for creating a novel therapeutic drug.	Antimi-crobial Activity	Buonocore et al., 2019	increased antibacterial activity against pathogens and improved selectivity against prokaryotic cells
Examine the antibacterial activity, immune system function, aquaculture uses, and anti-infective medication properties of the Ct-20534 antimicrobial peptide found in the Triton snail Charonia tritonis.	Experimental Method: Real-time fluorescence quantitative PCR (qPCR)	Species: Giant Triton snail *Charonia tritonis*,	*Charonia tritonis* highly expresses the antimicrobial peptide gene Ct-20534 in the proboscis. It inhibits *S. aureus* and other Gram-positive and Gram-negative bacteria. These peptides are essential for the snail's immune system and could be used in aquaculture to create anti-infective drugs, which would be advantageous for the aquaculture industry.	Antimi-crobial Activity	(Cen et al., 2023)	Confirmed antibacterial activity against gram-positive and negative bacteria
Characterize a novel antimicrobial peptide (AMP) derived from histone H2A in the mud crab Scylla paramamosain	Sequence analysis of histone H2A from Scylla paramamosain	Species: *Scylla paramamosain* Extract: Histone H2A	A 38-amino acid peptide named Sphistin was identified as an AMP with high antimicrobial activity against various pathogens, including important aquatic pathogens. Sphistin exhibited typical AMP features and exerted antimicrobial effects by disrupting bacterial cell membranes without cytotoxicity to crab haemolymphs	Antimi-crobial Activity	(Chen et al., 2015)	Confirmed antibacterial activity

Table 1 *(continue)*

Study Objective	Methods	Biological Sample	Main Findings	Activity	References	Effects
			or mammalian cells. This discovery introduces Sphistin as a potential aquaculture and veterinary medicine application candidate.			
To discover gut microbiome-derived antimicrobial peptides (AMPs) in zebrafish, targeting resistant bacteria such as K. pneumoniae, P. aeruginosa, S. aureus, E. coli, and B. cereus, and assess their therapeutic potential and binding characteristics using metagenomics, molecular modeling, and bioinformatics.	Experimental Method: Metagenomics, metabolic modeling, molecular modeling (docking and dynamics)	Gut microbiome of zebrafish	The study successfully identified prospective AMPs using the zebrafish gut microbiota. One in particular, "MPPYLHEIQPHTASNCQTELVIKL," showed promise due to its hydrophobic characteristics and stable binding to a target protein. These results present a novel method for creating AMPs that are effective against extremely resistant bacterial species.	Antimi-crobial Activity	(Gayathri et al., 2021)	Confirmed antibacterial activity against bacterial pathogens
To identify and study antimicrobial peptides (AMPs) in the Cuban freshwater snail Pomacea poeyana, including their chemical synthesis, structural analysis, effects on viral infections and cell toxicity, and antimicrobial activity against human pathogens.	Experimental Method: nanoLC-ESI-MS-MS technology and CD spectra analysis.	Cuban freshwater snail *Pomacea poeyana*	The study found two promising antimicrobial peptides (Pom-1 and Pom-2) in the Cuban freshwater snail *Pomacea poeyana*. Pom-1 showed potent antibacterial effects, while it had no anti-fungal activity. It also had low toxicity to human macrophages, making it a candidate for human antimicrobial use. Additionally, Pom-1 had a modest impact on HIV-1 infection and slightly inhibited the Zika virus.	Antimi-crobial Activity	(García et al., 2023)	Confirmed antibacterial activity for Pom-1 against bacterial pathogens

Table 1 *(continue)*

Study Objective	Methods	Biological Sample	Main Findings	Activity	References	Effects
To characterize two antimicrobial peptides derived from histone1 (LcH1) in Larimichthys crocea	Bioinformatics analysis, tissue distribution analysis, phylogenetic analysis, and scanning electron microscopy (SEM)	*Larimichthys crocea*	LcH1-derived peptides (LcH1–1 and LcH1–2) exhibit broad-spectrum antimicrobial activity, forming α-helix structures and damaging bacterial membranes. LcH1 expression increases in response to Cryptocaryon irritans infection, suggesting a role in the immune response and potential for disease control strategies.	Antimi-crobial Activity	(Ma et al., 2023)	Increased antibacterial activity of derived peptides
To discuss the anticancer properties of fish species Anabas testudineus antimicrobial peptides (AMPs). It specifically aims to find and assess these AMPs' effectiveness against the MCF7 and MDA-MB-231 breast cancer cell lines.	Experimental Method: Cytotoxicity Assay, that is, MTT Assay, examining gene expression (p53, BAX, BCL-2), caspase-3 activation, and conducting docking analysis and immunoprecipitation.	*Anabas testudineus* contains antimicrobial peptides (AMPs)	This study isolated two antimicrobial peptides (AtMP1 and AtMP2) with cytotoxic action against breast cancer cell lines from *Anabas testudineus* mucus. These peptides caused cell cycle arrest and apoptosis by upregulating p53, expressing the pro-apoptotic BAX gene, downregulating the anti-apoptotic BCL-2 gene, and activating caspase-3. Their association with target proteins was supported by computational analysis and immunoprecipitation, indicating their potential as cancer treatments.	Anticancer and Anti-microbial Activity	(Najm et al., 2021)	Confirmed antibacterial activity against bacterial pathogens
To examine and characterize SaRpAMP, an antimicrobial peptide isolated from the skin of Silurus asotus, a freshwater fish. The objective is to understand its structure, antibacterial activity, and mechanism of action.	Experimental Method: Primary structure analysis, cDNA cloning, secondary structure analysis, 3D modeling and antimicrobial activity testing.	Species: *Silurus asotus*	The research discovered SaRpAMP, an antimicrobial peptide with strong antibacterial activity and an amphiphilic structure, in the skin of *Silurus asotus*. SaRpAMP, the first generated from the C-terminal region of 60S ribosomal protein L27, interacts with bacterial membranes and may disrupt them, showing promise for battling bacterial infections.	Antimi-crobial Activity	(Oh et al., 2020)	Confirmed antibacterial activity against bacterial pathogens

Table 1 *(continue)*

Study Objective	Methods	Biological Sample	Main Findings	Activity	References	Effects
To find, describe, and investigate the potential of antimicrobial peptides (AMPs) from the skin mucus of the African catfish (Clarias gariepinus) as prospective substitutes for conventional antibiotics in a variety of applications.	Experimental Method: C (18) Solid-Phase Extraction (Purification), Agar Well Diffusion method, broth-dilution method, Sephadex G-25 gel filtration and Orbitrap Fusion Lumos Tribrid Mass Spectrometry (peptide identification)	Species: African Catfish (*Clarias gariepinus*)	Both *S. aureus* and *E. coli* were resistant to the antibacterial properties of the skin mucus from African catfish. With the lowest Minimum Inhibitory Concentration (MIC), the catfish from Lake Albert displayed the highest activity level. Seven brief AMPs with excellent antibacterial ratings and amphipathic properties were discovered through mass spectrometry investigation. These AMPs have the potential to replace conventional antibiotics in a variety of industries, but further investigation is required to determine how safe they are.	Antimi-crobial Activity	(Okella et al., 2021)	Confirmed antibacterial activity against bacterial pathogens
To investigate the expression, structure, interactions with membranes, biological effects, safety for mammalian cells, and antibacterial drug potential of trimetozine.	Experimental Methods: rtPCR, Circular dichroism spectroscopy, Fluorescence assays, Membrane studies, antimicrobial activity assessments, Cytotoxicity assays	Species: Antarctic fish *Trematomus bernacchii*, from which the AMP Trimetozine was identified and characterized	To demonstrate that trimetozine is an effective antibacterial peptide with the potential to become a novel therapeutic candidate. Through a carpet-like process, it demonstrates activity against a variety of pathogens, including Gram-negative bacteria. Trimetozine is comparable to other AMPs from Antarctic fishes in terms of its minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values against bacteria. Trimetozine is a possible option for further therapeutic development because it does not exhibit hemolytic or cytotoxic effects against mammalian cells at effective dosages against bacteria.	Antimi-crobial Activity	(Pelle et al., 2020)	Confirmed antibacterial activity against bacterial pathogens

Table 1 *(continue)*

Study Objective	Methods	Biological Sample	Main Findings	Activity	References	Effects
To evaluate the bioinformatics characterization and antimicrobial role of two piscidin (Pi) peptides identified from the transcriptome of Channa striatus.	Bioinformatics analysis; gene expression analysis with immune stimulants; antibiogram assay; minimum inhibitory concentration (MIC) and antibiofilm assays; flow cytometry analysis; scanning electron microscopy (SEM) imaging	Transcriptome of striped murrel *Channa striatus*	The study identified two antimicrobial peptides, CsRG12 and CsLC11, from CsPi. Gene expression analysis revealed induced expression patterns of CsPi with immune stimulants. CsRG12 and CsLC11 exhibited activity against multi-drug-resistant pathogens S. aureus and B. cereus, disrupting bacterial membrane formation as observed via flow cytometry and SEM imaging. These findings suggest CsPi's involvement in innate immunity and potential for therapeutic development in aquaculture biotechnology.	Antimi-crobial Activity	(Raju et al., 2020)	Confirmed antibacterial activity
To investigate Anisakis marine parasitic worm-derived antimicrobial peptides (anisaxins) for their efficacy as bactericidal agents, especially against multi-drug-resistant Gram-negative bacteria, while understanding their mechanism of action and selectivity against bacteria with minimal harm to human peripheral blood mononuclear cells (HPBMCs).	Experimental Method: solid-state NMR (ssNMR), molecular dynamics (MD) simulations (investigate peptide's mode of action) Atomic force microscopy and flow cytometry (membrane permeabilization and cytotoxicity)	Species: *Nematode Anisakis* Extract: anisaxins	The study discovered anisaxins, novel antimicrobial peptides made by the marine parasite *Anisakis* that have strong bactericidal action, especially against Gram-negative bacteria that are multi-drug resistant. Anisaxins interact with bacterial membranes, producing lipid extraction and membrane bulging, which kills the bacteria by preventing cell division. These peptides do not cause much cytotoxicity in human cells, which is significant since they suggest they will make good candidates for future antimicrobial medication development during antibiotic resistance.	Antimi-crobial Activity	(Rončević et al., 2022)	Confirmed antibacterial activity against bacterial pathogens

Table 1 *(continue)*

Study Objective	Methods	Biological Sample	Main Findings	Activity	References	Effects
To characterize two piscidin-like antimicrobial peptides (LjPL-3 and LjPL-2) isolated from Japanese sea bass (Lateolabrax japonicus) and investigate their role in the innate immune response, particularly their antimicrobial activity and modulation of immune cell functions.	Isolation and characterization of LjPL-3 and LjPL-2 from Japanese sea bass; examination of their expression, antimicrobial activity, and immune modulation.	Species: Japanese sea bass (*Lateolabrax japonicus*) Extract: LjPL-3 and LjPL-2	LjPL-3 and LjPL-2, isolated from Japanese sea bass, exhibit differential tissue expression and are upregulated after Vibrio harveyi infection. They display distinct antimicrobial spectra, while treatment decreases inflammatory cytokine production and enhances immune cell functions. LjPL-2 shows bacterial killing capability in monocytes/macrophages, and administration enhances fish survival post-infection, reducing bacterial burden.	Antimi-crobial Activity	(Wu et al., 2023)	Increased antibacterial activity against aquatic pathogens
Investigate the antimicrobial activity of moricin-like peptides (MLPs) from Antheraea pernyi against Vibrio pathogens in aquatic animals, particularly sea cucumbers.	Bioinformatics analysis, heterologous expression using the AnpeNPV bacmid system, and purification from *A. pernyi* pupae	Species: *A. pernyi* Extract: rAnpe-MLP1	Recombinant Anpe-MLP1 exhibited antimicrobial activity against gram-positive *Staphylococcus aureus*, gram-negative *Escherichia coli*, and three Vibrio species. It effectively inhibited wild-type Vibrio fluvialis infections in sea cucumbers, suggesting its potential as a novel anti-infective agent for aquaculture.	Antimi-crobial Activity	(Ye et al., 2024)	Confirmed antibacterial activity against aquatic pathogens
To identify novel antimicrobial peptides (AMPs) derived from subunits of Tegillarca granosa hemoglobin (Hb) and evaluate their antibacterial activity against various bacteria strains	Bioinformatics prediction, synthetic synthesis of peptides, minimum inhibitory concentration (MIC) assays	Species: *Tegillarca granosa* Extract: mTgHbP7	A mutant *T. granosa* hemoglobin peptide (mTgHbP7) exhibited significant antibacterial activity against *Vibrio alginolyticus*, *V. parahaemolyticus*, and *Escherichia coli*. mTgHbP7 demonstrated an α-helical structure, characteristic of bactericidal AMPs, and exhibited no cytotoxicity to mammalian cells, even at high concentrations. These findings offer insights into the potential of mollusk hemoglobin-derived AMPs for developing antimicrobial agents.	Antimi-crobial Activity	(Zheng et al., 2022)	Increased antibacterial activity of the modified peptide

RESULT AND DISCUSSION

After screening the titles and abstracts, 922 of these articles were removed as they were published before 2014 (Figure 1). Studies with titles and abstracts unsuitable for the review's eligibility criteria and aims are also excluded. A total of 34 journal articles were evaluated, and 12 were disqualified because they contained synthesized peptides (n=4), lacked anticancer or antimicrobial effects (n=2), or came from sources other than aquatic life (n=6).

Antimicrobial Peptides from Aquatic Organism

The reviewed papers show the types, modes of action, potential benefits and the sources of the derived AMPs. The presence of AMPs among all aquatic organisms shows that they provide a first barrier of protection against a multitude of microbial pathogens (Baiden et al., 2023; Buonocore et al., 2019; Cen et al., 2023; García et al., 2020), with hundreds of AMPs being discovered and identified from both plants and animals (Najm, 2021). Among the identified AMPs, most sources come from marine life, including fish, crustaceans, and marine plants (Anbuchezian et al., 2018; Baiden et al., 2023; García-Beltrán et al., 2023). It is due to the living conditions that contain a lot of free-floating microbes that also harbor potential pathogenic microorganisms, resulting in the need for high amounts of AMPs to protect marine life against infections and disease (Najm et al., 2021).

From this systematic review, a total of 18 aquatic life species including fish, aquatic plants, and nematodes, were reported to produce AMPs based on in-vitro study results, including *Danio rerio* (Gayathri et al., 2021), *Phaeodactylum tricornutum* (Anbuchezian et al., 2018), *Sebastiscus marmoratus* (Bo et al., 2019), *Chionodraco hamatus* (Buonocore et al., 2019), *Charonia tritonis* (Cen et al., 2023), *Scylla paramamosain* (Chen et al., 2015), *Pomacea poeyana* (García et al., 2020), *Larimichthys crocea* (Ma et al., 2023), *Anabas testudineus* (Najm et al., 2021), *Silurus asotus* (Oh et al., 2020), *Clarias gariepinus* (Okella et al., 2021), *Trematomus bernacchii* (Pelle et al., 2020), *Channa striatus* (Raju et al., 2020), *Nematode anisakis* (Rončević et al., 2022), *Lateolabrax japonicus* (Wu et al., 2023), *Antheraea pernyi* (Ye et al., 2024), *Tegillarca granosa* (Zheng et al., 2022).

Classification of AMPs

One of the most promising antibiotic alternatives is antimicrobial peptides, which can treat bacterial infections, particularly those brought on by multi-drug-resistant pathogens (Rima et al., 2021). AMPs, also known as host defense peptides (HDPs), are a component of the innate immune response in all kinds of life (Ganz, 2002). Various organisms naturally create them as a defense mechanism against pathogens, including bacteria, viruses, and fungi that invade the body (Zasloff, 2007). The antibacterial activity of AMPs is broad-spectrum, making them useful against a variety of pathogens. They can damage an organism's cell membrane, causing it to lyse or burst open, which kills the creature. It led to a big discovery and one of the potential antibiotic replacements.

AMPs have been categorized according to several factors, including their origin, structure, method of action, and amino acid makeup. These divisions aid in designing and developing new medicinal drugs to fight infectious diseases and understanding the diversity and complexity of AMPs (Hafeez et al., 2021). Figure 2 shows the classification of AMPs based on their biological activity, sources/origin, and the difference between natural and synthetic antimicrobial peptides.

Based on their origin, antimicrobial peptides from marine life can be divided into different groups. This classification distinguishes different marine AMP sources. For example, fish-derived AMPs come from Tilapia species, while mollusk-derived AMPs are obtained from marine creatures like sea hares and snails (Peng et al., 2012). The biodiversity-rich sponges also produce AMPs that are generated from them, and marine algae contribute to this classification by creating AMPs that have antibacterial capabilities. These peptides are available from different marine sources in different numbers and with different properties.

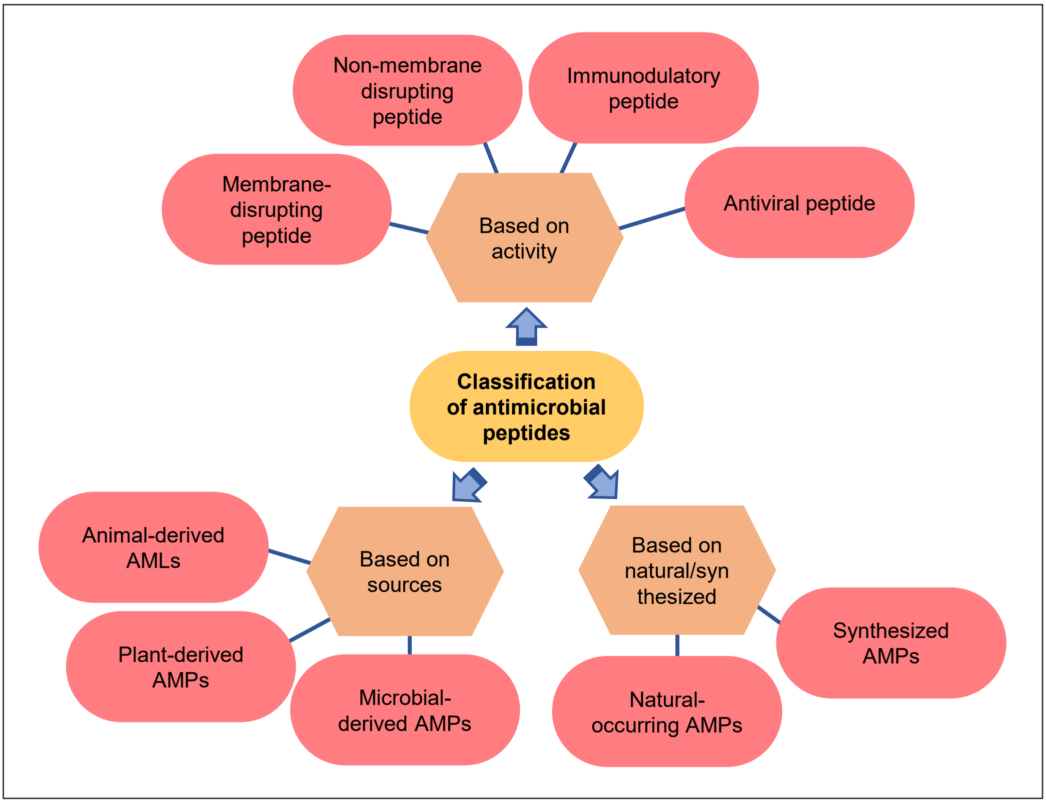

Figure 2. Classification of AMPs based on their biological activity, sources/origin, and the difference between natural and synthetic antimicrobial peptides

Marine-derived AMPs are categorized using a structure-based approach that considers their structural characteristics. As with Magainin, linear AMPs have a straightforward, linear structure without disulfide links. Contrarily, cyclic AMPs like pardaxin frequently create a cyclic or ring structure due to disulfide bonds. Like LL-37, several AMPs have a mostly helical secondary structure, whereas tachyplesin adopts a -sheet shape. These structural differences shed light on the actions they might take (Falanga et al., 2016).

Another classification takes into account how AMPs work, that is, their mode of action. Some peptides are particularly recognized for rupturing the membranes of bacterial cells, which causes cell lysis and bacterial death; this refers to membrane-disrupting AMPs. Others exert their impact differently, like interfering with intracellular functions, which refers to non-membrane-disrupting AMPs (Semreen et al., 2018). It is crucial to understand their primary mechanisms of action to evaluate their prospective applications and therapeutic use.

The origin of AMPs is another way to classify them, with natural AMPs coming straight from marine species. As opposed to their natural counterparts, synthetic AMPs are created and produced based on their structures and characteristics to improve their activity, stability, or other characteristics (Lei et al., 2019). These modifications, intended to improve activity, stability, or other desired qualities, may involve changes to the peptide's sequence, amino acid content, or structural features. Through the customization of these artificial analogs, scientists can adjust their biological characteristics to tackle certain issues like cancer treatment or resistance to antibiotics (Wang et al., 2023). It will be referred to as synthetic analog classification. Synthesized AMPs are created in a laboratory, but naturally occurring AMPs are created by living things as a part of their natural defensive mechanism. Synthesized AMPs may function more effectively as therapeutic agents if they possess particular qualities, such as improved potency or selectivity. It has also been found that synthesized AMPs are generally more stable and possess a longer half-life as compared to naturally occurring AMPs (Baharin et al., 2021; Büyükkiraz & Kesmen, 2022; Lei et al., 2019). This characteristic highlights the potential superiority of synthetic AMPs in therapeutic settings, providing increased durability and longevity.

Mode of Actions Towards Microbes

AMPs exert their effects by compromising the integrity of the bacterial cell membrane or impeding vital cellular functions, including protein synthesis and DNA replication. The precise manner of action differs depending on the particular peptide and the target microorganism (Lei et al., 2019). As will be covered below in Figure 3, they can affect microorganisms in a variety of ways.

The breakdown of the microbial cell membrane is one frequent method. As AMPs insert into membranes, they can create pores or channels, causing intracellular contents to spill, ultimately causing microbial death (Lei et al., 2019). Certain AMPs can also prevent the synthesis of proteins by attaching to ribosomes during the termination of translation, interfering with the synthesis of proteins (Huan et al., 2020). Inhibiting bacterial growth and proliferation may result from this. They can even prevent DNA and RNA synthesis by attaching to bacterial genomes (Huan et al., 2020).

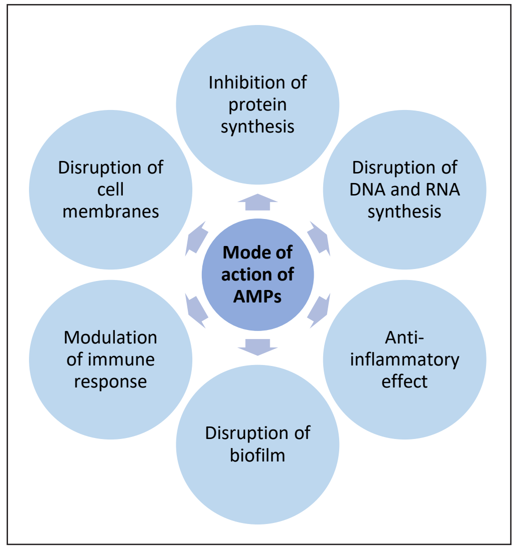

Figure 3. Different types of modes of action of antimicrobial peptides towards microbes

By activating or inhibiting immune cells, other AMPs can modify the immunological response and increase the clearance of infections. For instance, some AMPs can activate macrophages, which are important immune cells in phagocytosis and the eradication of invasive microbes (Mahlapuu et al., 2016). The production of pro-inflammatory cytokines can be inhibited by other AMPs, which can lessen tissue damage and encourage healing when an infection is present (Méndez-Samperio, 2013).

Also, it has been demonstrated that some AMPs can dislodge biofilms, which are intricate colonies of microorganisms that are challenging to treat with conventional antibiotics. Biofilms can develop on surfaces like medical implants and are linked to persistent illnesses that are challenging to treat. Certain AMPs have been discovered to prevent biofilms' development or damage the matrix that binds them together, which causes the biofilm to break down and makes bacteria more vulnerable to antimicrobial agents (Batoni et al., 2016).

Moreover, some AMPs have anti-inflammatory properties that may lessen tissue damage and encourage healing when an infection is present. Although inflammation plays a crucial role in the immune response and is a typical reaction to infection, it can also cause tissue damage and increase the severity of the illness. It has been discovered that some AMPs have anti-inflammatory properties that can aid in reducing tissue damage and encouraging recovery (Luo & Song, 2021).

In conclusion, AMPs are a variety of chemicals that affect bacteria in a variety of ways. One reason AMPs are efficient against a variety of microbes and can potentially be an important weapon in the fight against antimicrobial resistance is their capacity to function through numerous routes (Luo & Song, 2021).

Figure 4 shows the different modes of action via electrostatic interactions used by AMPs towards the bacterial membranes' inhibition of bacterial growth, which prevents

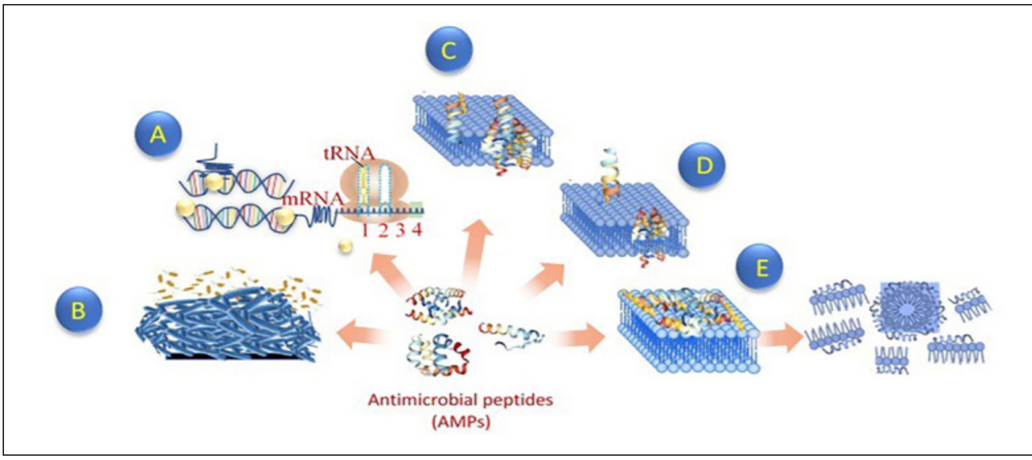

Figure 4. Mode of actions of AMPs against microbes (Mba & Nweze, 2022)

the host bacteria from developing resistance against the AMPs. Based on the type of AMP, they are able to disrupt intercellular processes such as protein synthesis, which alters enzymatic and cell signaling activities, as seen in (A). Some AMPs possess the ability to disrupt biofilm formation, as seen in (B), which is one of the defense mechanisms of some bacteria. As for AMPs that disrupt the bacterial membrane, there are three categories of modes of action that have been identified, with the first being the Barrel stave model, as seen in (C), where the AMPs aggregate together to form a tube and are arranged parallel to the phospholipid bilayer to form a channel. The Toroidal pore model (D) acts similarly to the Barrel stave model, where the AMPs are arranged parallel to the phospholipid bilayer to form a channel, with the difference being that with the Toroidal pore model, there are no lateral interactions between the peptides in the formation of the channel. Finally, for the Carpet model (E), the AMPs are scattered throughout the bacterial membrane like a carpet and, at a high enough concentration, will exhibit a detergent-like behavior where sections of the phospholipid bilayer are pulled away in a globular shape (Mba & Nweze, 2022).

Antibacterial, Antiviral, and Anti-Inflammatory Activities of Marine-derived Peptides

Antibacterial peptides from marine life have a variety of biological functions with exceptional promise for therapeutic uses. Because of their antibacterial, antiviral, and anti-inflammatory properties, they can defend against a variety of health risks (Kang et al., 2015).

Antibacterial Activity

These peptides are skilled at locating and damaging bacterial cell membranes, eliminating pathogenic bacteria. Peptides from the marine environment have demonstrated notable antibacterial activity in their natural forms and as-synthesized analogs.

For instance, the natural antibacterial peptides AtMP1 and AtMP2, produced in the epidermal mucus of the *Anabas testudineus* fish, have shown stronger antibacterial activity against both gram-positive and gram-negative pathogenic bacteria than conventional antibiotics (Najm et al., 2021).

In addition to naturally occurring peptides, synthetic analogs inspired by their marine counterparts were also created. A notable example of a synthetic peptide with potent antibacterial properties derived from AtMP1 is AtMP5, which showed significant improvements in antibacterial properties compared to its original counterpart (Law et al., 2023). These synthetic counterparts serve as an example of how technological advancements might harness the power of peptides originating from marine sources and improve those compounds' efficacy against a variety of bacterial diseases (Hallock et al., 2003).

Antiviral Activity

Some peptides of marine origins may prohibit viruses from replicating and infecting host cells. Figure 5 shows the horseshoe crab *Tachypleus tridentatus* peptide tachyplesin, a marine antimicrobial cell-penetrating peptide, as an anti-HBV agent, exhibits antiviral action against a variety of viruses, including HIV and the herpes simplex virus (Narula et al., 2023). Enfuvirtide has played a key role in the management of HIV infections by obstructing the virus's entry into immune cells and limiting its capacity to spread infection. The natural antiviral properties of marine peptides inspired it. The success of these synthetic antiviral medications demonstrates the important role that marine-derived peptides play in creating treatments for some of the most difficult viral illnesses (Narula et al., 2023).

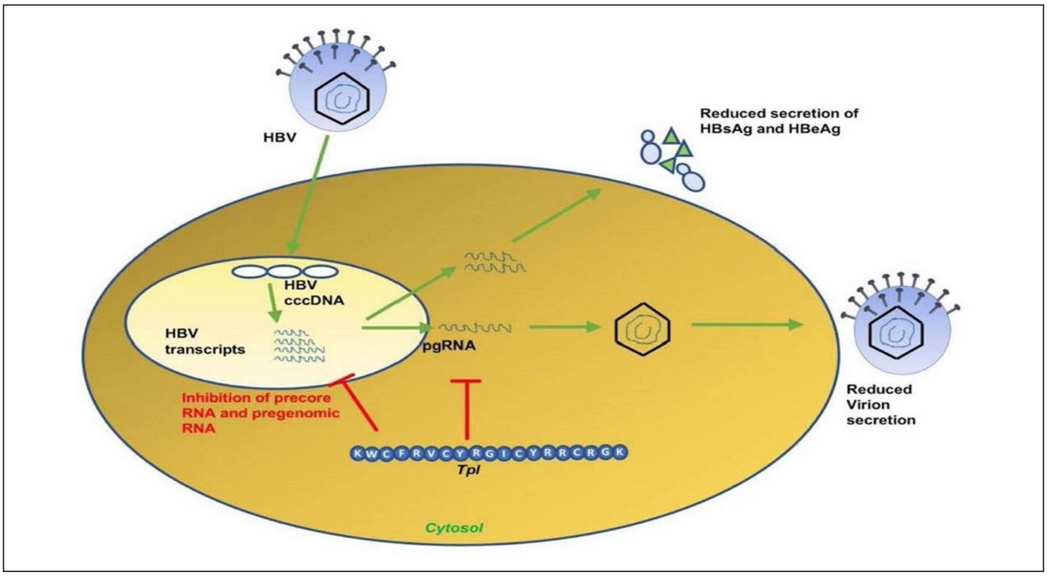

Figure 5. Tpl's anti-HBV efficacy at non-cytotoxic dosages demonstrates a potent therapeutic peptide for HBV (Narula et al., 2023)

These findings emphasize the value of investigating diverse marine life for potential remedies to problems with world health and the value of comprehending the mechanisms underlying these extraordinary antiviral marine peptides.

Anti-inflammatory Activities

Many peptides of marine origins are anti-inflammatory, reducing inflammation and its associated discomfort. In the blood of marine species, a peptide called Hemorphin has antibacterial and anti-inflammatory properties. Controlling the immune response can reduce inflammation, making it useful for future anti-inflammatory drugs (Nyberg et al., 2013). Such peptides may facilitate the creation of brand-new anti-inflammatory medications.

Hemorphin's combined abilities to fight bacterial threats and reduce inflammation highlight its potential importance in creating new anti-inflammatory medications (Nyberg et al., 2013). Researchers trying to discover these peptides' medicinal potential remain fascinated by the marine environment and its tremendous variety.

Studies of AMPs on Therapeutic Research

Studies demonstrate the effects of AMPs on microorganisms. Most AMPs found in marine invertebrates, such as arthropods, mollusks, and cnidarians, are cationic and hydrophobic, and they specifically target vital elements of microbial cell walls and membranes. It dictates the range of activity of these AMPs. For AMPs from marine invertebrates, a wide variety of modes of action have been reported and discussed in detail for several families. For instance, mollusk defensins bind to lipid II, the precursor of peptidoglycan, and are primarily effective against Gram-positive bacteria. Both mollusk bactericidal/permeability-increasing protein (BPI) and arthropod anti-lipopolysaccharide factors (ALFs), which are mostly active against Gram-negative bacteria, bind to lipopolysaccharide (LPS). Lastly, the exclusively anti-fungal crustacean PvHCt permeabilizes the fungal plasma membrane (Destoumieux-Garzón et al., 2016).

In another research shown in Figure 6, the antimicrobial peptide in the epidermal mucus of *Anabus testudineus*, a sturdy freshwater fish, was tested in its microbial activity. Both epidermal mucus and streptomycin have antibacterial effects on pathogenic bacteria, such as *P. aeruginosa*, *E. coli*, *B. subtilis*, and *B. cereus*, which have undergone triplicate. It was revealed that EM has a lower MIC (62.5 g/mL) than streptomycin (125 g/mL) for inhibiting the development of *P. aeruginosa* and *E. coli*. Bivariate analysis was performed in the correlation analysis, which produced significant results (p 0.01) between EM and the control (streptomycin) for the pathogens *E. coli* and *P. aeruginosa*. This finding corroborated the findings of Wei et al. (2010), who discovered that *P. aeruginosa* and other Gram-negative bacteria are more susceptible to the antibacterial effects of snakehead fish.

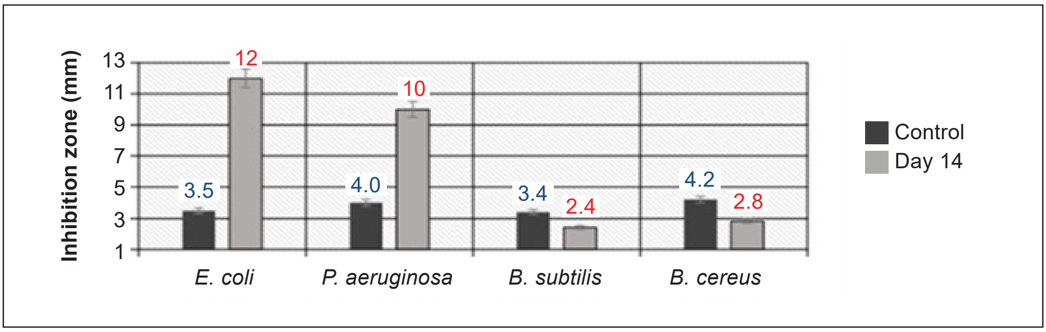

Figure 6. The sample used as a control included streptomycin and was undergone triplicate (Najm et al., 2021)

It might aid both species' capacity to endure in contaminated water (Najm et al., 2021). Further research on the naturally occurring peptides via modification has also shown that modifying AMPs can increase antibacterial activity, such as AtMP5 (Law et al., 2023). Besides that, both studies have found that the AMPs derived from the Anabas testudineus fish have the ability to function as an antiproliferative agent against breast cancer cells, thus also categorizing the peptides as having dual activities, namely antibacterial and anticancer (Law et al., 2023; Najm et al., 2021).

Therapeutics

Antimicrobial peptides (AMPs) have been studied extensively for their potential therapeutic applications. In addition to their direct antimicrobial activity, AMPs have been found to have a range of other biological properties, including anti-inflammatory, wound healing, and immunomodulatory effects. These properties make AMPs attractive candidates for developing novel therapeutics (Giuliani et al., 2007).

It takes a multidisciplinary team effort involving cooperation between biotechnology businesses, academics, and marine science experts to develop synthetic marine-derived AMPs for therapeutic reasons. It entails creating artificial replicas of the natural peptides while guaranteeing their bioavailability, stability, and efficient delivery to the infection site. Some examples of AMP-derived therapeutics have been developed or are in various stages of development. Pexiganan: It is a synthetic version of the frog skin peptide magainin. Pexiganan is used to treat diabetic foot ulcers caused by bacterial infections. It works by disrupting bacterial membranes and is effective against a variety of Gram-positive and Gram-negative bacteria (Lipsky et al., 2008). Besides Pexiganan, there is also Brilacidin, a synthetic AMP with broad-spectrum activity against bacteria, viruses, and fungi. Brilacidin is being developed to treat infections, including acute bacterial skin and skin structure infections, oral mucositis, and inflammatory bowel disease (Brilacidin). More AMP-based treatments will likely become available as research in this area continues.

Future Potential of Antimicrobial Peptides

Future research should include medium to long-term randomized clinical trials to confirm the effect of peptides on disease and test their efficacy in increasing resistance to chronic diseases. As a result, additional research is needed to link the benefits of AMP, its peptidomimetics, and antibiotics to drug resistance reduction (Cipolari et al., 2020). Fish-derived AMPs have been proposed as a future therapeutic strategy (Chee et al., 2019). Further and continuous research into synthesizing and characterizing these peptides is critical to ensuring their efficacy and usability. AMPs derived from fish have shown promise as therapeutic strategies. Recent research into *in-silico* modifications of these AMPs has also shown promising results with increased antibacterial activity as well as increased robustness and stability, which needs to be further studied to fully take advantage of these natural resources in the battle against antibiotic resistance (Law et al., 2023).

In-silico predictions and modifications of AMPs are at the forefront of AMP modification due to their ability to accurately predict how the changes in peptide sequence affect the structure, net charge, hydrophobicity as well as stability of the peptide (Law et al., 2023). One of the biggest open-source AMP databases, known as the Collection of Antimicrobial Peptides (CAMP), is commonly used for the identification and prediction of AMPs used in peptide modifications (Law et al., 2023; Najm et al., 2021; Waghu & Idicula-Thomas, 2019).

Limitations

Antimicrobial peptides (AMPs) have been shown to have great potential as therapeutics. However, several concerns must be addressed before they can be utilized for human therapies. One such concern is their toxicity, as excessive amounts of certain AMPs can harm mammalian cells. For example, melittin in bee venom shows high hemolytic effects at high concentrations (Jenssen et al., 2006).

Another concern would be the specialization of AMPs towards a specific pathogen. As AMPs are able to target a wide range of microorganisms, it must be seen that the AMPs are built to target a specific pathogen instead of random targeting of microorganisms, which could adversely affect the natural microbiota, leading to unforeseen problems (Lazzaro et al., 2020). The stability of the AMPs also poses a concern as they can easily be broken down by enzymes and proteases within the body or even environmental factors such as temperature and pH, which would lead to a decrease in their therapeutic potency (Tortorella et al., 2023).

The cost of research and development and industrial manufacturing poses a concern within the medicinal industry due to the specificity of the amino-acid sequence buildup and storage of the AMPs, which would be costly to build and maintain a framework of machinery and downstream processing procedures. It would limit the availability and affordability of the AMPs or even make it financially unviable for large-scale manufacturing

(Jenssen et al., 2006). Moreover, there have also been discoveries showing that some microbes have developed defense mechanisms against AMPs, which has reduced the efficacy of the AMPs, much like how microbes have developed resistance towards conventional antibiotics. Therefore, much more research is needed to be performed on the modification of naturally-derived AMPs to counter such resistance from microbes in order to increase their efficacy and shelf life (Jenssen et al., 2006)

These concerns and limitations must be considered, and steps taken to overcome them to fully utilize the promising potential of AMPs in therapeutics. From this review study, ongoing research is being carried out to overcome these hurdles and maximize the potential of AMPs for therapeutic uses. Some AMPs derived from marine organisms might be key to addressing these concerns. As marine life adapts to its ever-changing environments, researchers are able to gain insights into how nature is adapting these AMPs to suit the environment. In summary, research into AMPs derived from marine animals holds an untapped source of potential for overcoming existing limitations and concerns surrounding antibiotic resistance.

CONCLUSION

This systematic review examined 952 research articles on antimicrobial peptides from marine species and thoroughly summarized the field's current understanding. Twenty-one articles were carefully analyzed, and the results showed a notable distribution between review journals and in-vitro studies: 11 articles were devoted to in-vitro investigations, and 10 articles were added to the discussion by providing in-depth reviews of antimicrobial peptides in aquatic organisms.

The comprehensive review of these compounds showcases the types, mode of action, and prospective advantages of antimicrobial peptides (AMPs) generated from marine species. With hundreds of AMPs found in plant and animal sources, their presence provides an essential first line of defense against microbial infections in a wide spectrum of marine organisms. The abundance of AMPs in these creatures, primarily derived from marine life such as fish, crabs, and marine plants, is a reaction to the harsh living conditions marked by a multitude of free-floating bacteria and potentially harmful microorganisms.

The systematic review highlights 12 aquatic species, such as *Phaeodactylum tricornutum* (Anbuchezian et al., 2018), *Chionodraco hamatus* (Buonocore et al., 2019), *Charonia tritonis* (Cen et al., 2023), *Pomacea poeyana* (García et al., 2020), *Danio rerio* (Gayathri et al., 2021), *Anabas testudineus* (Najm et al., 2021), *Silurus asotus* (Oh et al., 2020), *Clarias gariepinus* (Okella et al., 2021), *Trematomus bernacchii* (Pelle et al., 2020), and *Nematode anisakis* (Rončević et al., 2022). It is reported to produce AMPs based on in-vitro studies, emphasizing the promising potential of marine-derived AMPs for developing novel and effective antimicrobial agents.

Although effective antimicrobial drugs have been developed thanks to advances in synthetic peptide design, more study is essential to discovering new peptides and improving our comprehension of their actions. The results of this systematic review highlight the need for continuing research into and utilization of the enormous potential of synthetic antimicrobial peptides derived from the rich and diverse marine ecosystem. They also highlight the significance of marine life as a source of inspiration for creative antimicrobial solutions.

ACKNOWLEDGEMENT

This work is supported by Malaysia Ministry of Higher Education (MOHE) under FRGS grant: FRGS/1/2022/STG01/INTI/02/3 and FRGS/1/2023/STG01/UKM/02/5

REFERENCES

Anbuchezian, R., Ravichandran, S., Karthick Rajan, D., Tilivi, S., & Prabha Devi, S. (2018). Identification and functional characterization of antimicrobial peptide from the marine crab Dromia dehaani. *Microbial Pathogenesis*, *125*, 60–65. https://doi.org/https://doi.org/10.10 16 /j.micpath.2018.08.056

Baiden, N., Gandini, C., Goddard, P., & Sayanova, O. (2023). Heterologous expression of antimicrobial peptides S-thanatin and bovine lactoferricin in the marine diatom Phaeodactylum tricornutum enhances native antimicrobial activity against Gram-negative bacteria. *Algal Research*, *69*, Article 102927. https://doi.org/10.1016/j.algal.2022.102927

Batoni, G., Maisetta, G., & Esin, S. (2016). Antimicrobial peptides and their interaction with biofilms of medically relevant bacteria. *Biochimica et Biophysica Acta (BBA) - Biomembranes, 1858*(5), 1044-1060. https://doi.org/10.1016/j.bbamem.2015.10.013

Bo, J., Yang, Y., Zheng, R., Fang, C., Jiang, Y., Liu, J., Chen, M., Hong, F., Bailey C. Segner, H., & Wang, K. (2019). Antimicrobial activity and mechanisms of multiple antimicrobial peptides isolated from rockfish Sebastiscus marmoratus. Fish & Shellfish Immunology, 93,1007-1017. https://doi.org/10.1016/j.fsi.2019.08.054

Buonocore, F., Picchietti, S., Porcelli, F., Della Pelle, G., Olivieri, C., Poerio, E., Bugli, F., Menchinelli, G., Sanguinetti, M., Bresciani, A., Gennari, N., Taddei, A. R., Fausto, A. M., & Scapigliati, G. (2019). Fish-derived antimicrobial peptides: Activity of a chionodracine mutant against bacterial models and human bacterial pathogens. *Developmental & Comparative Immunology*, *96*, 9–17. https://doi.org/10.1016/j.dci.2019.02.012

Büyükkiraz, M. E., & Kesmen, Z. (2022). Antimicrobial peptides (AMPs): A promising class of antimicrobial compounds. *Journal of Applied Microbiology, 132*(3), 1573-1596.https://doi.org/10.1111/jam.15314

Cen, X., Liu, B., Zhang, G., Liu, H., Yao, G., He, M., & Liu, W. (2023). Antimicrobial peptide in giant *Triton* snail *Charonia* tritonis: mRNA profiles for tissues and its potential antibacterial activity. *Fish & Shellfish Immunology*, *136*, Article 108734. https://doi.org/https://doi.org/ 10.1016/ j.fsi.2023.108734

Chang, S. M., Matchar, D. B., Smetana, G. W., & Umscheid, C. A. (Eds.). (2012). *Methods guide for medical test reviews.* Agency for Healthcare Research and Quality.

Chee, P. Y., Mang, M., Lau, E. S., Tan, L. T. H., He, Y. W., Lee, W. L., Pusparajah, P., Chan, K., Lee, L., & Goh, B. H. (2019). Epinecidin-1, an antimicrobial peptide derived from grouper (Epinephelus coioides): Pharmacological activities and applications. *Frontiers in microbiology, 10*, Article 2631. https://doi.org/10.3389%2Ffmicb.2019.02631

Chen, B., Fan, D. Q., Zhu, K. X., Shan, Z. G., Chen, F. Y., Hou, L., Cai, L., & Wang, K. J. (2015). Mechanism study on a new antimicrobial peptide Sphistin derived from the N-terminus of crab histone H2A identified in haemolymphs of *Scylla paramamosain*. *Fish & Shellfish Immunology, 47*(2), 833–846. https://doi.org/10.1016/j.fsi.2015.10.010.

Cipolari, O. C., de Oliveira Neto, X. A., & Conceição, K. (2020). Fish bioactive peptides: A systematic review focused on sting and skin. *Aquaculture, 515*, Article 734598. https://doi.org/10.1016/j.aquaculture.2019.734598

Destoumieux-Garzón, D., Rosa, R. D., Schmitt, P., Barreto, C., Vidal-Dupiol, J., Mitta, G., Gueguen, Y., & Bachere, E. (2016). Antimicrobial peptides in marine invertebrate health and disease. *Philosophical Transactions of the Royal Society B: Biological Sciences, 371*(1695), Article 20150300. https://doi.org/10.1098%2Frstb.2015.0300

Falanga, A., Lombardi, L., Franci, G., Vitiello, M., Iovene, M. R., Morelli, G., Galdiero, M., & Galdiero, S. (2016). Marine antimicrobial peptides: Nature provides templates for the design of novel compounds against pathogenic bacteria. *International Journal of Molecular Sciences*, *17*(5), Article 785. https://doi.org/10.3390/ijms17050785

Ganz, T. (2002). Antimicrobial polypeptides in host defense of the respiratory tract. *The Journal of Clinical Investigation, 109*(6), 693-697. https://doi.org/10.1172/JCI15218

García-Beltrán, J. M., Arizcun, M., & Chaves-Pozo, E. (2023). Antimicrobial peptides from photosynthetic marine organisms with potential application in aquaculture. *Marine Drugs, 21*(5), Article 290. https://doi.org/10.3390/md2 21(5), 290. 1050290

Gayathri, K. V., Aishwarya, S., Kumar, P. S., Rajendran, U. R., & Gunasekaran, K. (2021). Metabolic and molecular modelling of zebrafish gut biome to unravel antimicrobial peptides through metagenomics. *Microbial Pathogenesis*, *154*, Article 104862. https://doi.org/10.1016/j.micpath.2021.104862

Giuliani, A., Pirri, G., & Nicoletto, S. (2007). Antimicrobial peptides: An overview of a promising class of therapeutics. *Central European Journal of Biology*, *2*(1), 1-33. https://doi.org/10.2478/s11535-007-0010-5

Hafeez, A. B., Jiang, X., Bergen, P. J., & Zhu, Y. (2021). Antimicrobial peptides: An update on classifications and databases. *International Journal of Molecular Sciences, 22*(21), Article 11691. https://doi.org/10.3390/ijms222111691

Hallock, K. J., Lee, D. K., & Ramamoorthy, A. (2003). MSI-78, an analogue of the magainin antimicrobial peptides, disrupts lipid bilayer structure via positive curvature strain. *Biophysical Journal*, *84*(5), 3052-3060. https://doi.org/10.1016/S0006-3495(03)70031-9

Huan, Y., Kong, Q., Mou, H., & Yi, H. (2020). Antimicrobial peptides: Classification, design, application and research progress in multiple fields. *Frontiers in Microbiology*, *11*, Article 2259. https://doi.org/10.3389/fmicb.2020.582779

Jenssen, H., Hamill, P., & Hancock, R. E. (2006). Peptide antimicrobial agents. *Clinical Microbiology Reviews, 19*(3), 491-511. https://doi.org/10.1128%2FCMR.00056-05

Kang, H. K., Seo, C. H., & Park, Y. (2015). Marine peptides and their anti-infective activities. *Marine Drugs, 13*(1), 618-654. https://doi.org/10.3390/md13010618

Law, D., Najm, A. A., Chong, J. X., K'ng, J. Z., Amran, M., Ching, H. L., Wong, R. R., Leong, M. H., Mahdi, I. M., & Fazry, S. (2023). In silico identification and in vitro assessment of a potential anti-breast cancer activity of antimicrobial peptide retrieved from the ATMP1 anabas testudineus fish peptide. *PeerJ*, *11,* Article e15651. https://doi.org/10.7717/peerj.15651

Lazzaro, B. P., Zasloff, M., & Rolff, J. (2020). Antimicrobial peptides: Application informed by evolution. *Science*, *368*(6490), Article eaau5480. https://doi.org/10.1126/science.aau5480

Lei, J., Sun, L., Huang, S., Zhu, C., Li, P., He, J., Mackey, V., Coy, D. H., & He, Q. (2019). The antimicrobial peptides and their potential clinical applications. *American Journal of Translational Research*, *11*(7), Article 3919

Lipsky, B. A., Holroyd, K. J., & Zasloff, M. (2008). Topical versus systemic antimicrobial therapy for treating mildly infected diabetic foot ulcers: A randomized, controlled, double-blinded, multicenter trial of pexiganan cream. *Clinical Infectious Diseases. 47*(12), 1537-1545. https://doi.org/10.1086/593186.

Luo, Y., & Song, Y. (2021). Mechanism of antimicrobial peptides: Antimicrobial, anti-inflammatory and antibiofilm activities. *International Journal of Molecular Sciences, 22*(21), Article 11404. https://doi.org/10.3390/ijms222111401

Ma, H., Yang, L., Tian, Z., Zhu, L., Peng, J., Fu, P., Xiu, J., & Guo, G. (2023). Antimicrobial peptide AMP-17 exerts anti–Candida albicans effects through ROS-mediated apoptosis and necrosis. *International Microbiology, 26*(1), 81-90. https://doi.org/10.1007/s10123-022-00274-5.

Mahlapuu, M., Håkansson, J., Ringstad, L., & Björn, C. (2016). Antimicrobial peptides: An emerging category of therapeutic agents. *Frontiers in Cellular and Infection Microbiology*, *6*, Article 235805. https://doi.org/10.3389/fcimb.2016.00194

Mba, I. E., & Nweze, E. I. (2022). Antimicrobial peptides therapy: An emerging alternative for treating drug-resistant bacteria. *The Yale Journal of Biology and Medicine*, *95*(4), 445–463.

Méndez-Samperio, P. (2013). Recent advances in the field of antimicrobial peptides in inflammatory diseases. *Advanced Biomedical Research*, *2*(1), Article 50. https://doi.org/10.4103/2277-9175.114192

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *BMJ*, *339*, Article b2535. https://doi.org/10.1136/bmj.b2535

Moretta, A., Scieuzo, C., Petrone, A. M., Salvia, R., Manniello, M. D., Franco, A., Lucchetti, D., Vassallo, A., Vogel, H., Sgambato, A., & Falabella, P. (2021). Antimicrobial peptides: A new hope in biomedical and pharmaceutical fields. *Frontiers in Cellular and Infection Microbiology*, *11*, Article 668632. https://doi.org/10.3389/fcimb.2021.668632

Munn, Z., Moola, S., Lisy, K., Riitano, D., & Tufanaru, C. (2015). Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *International Journal of Evidence-based Healthcare*, *13*(3), 147–153. https://doi.org/10.1097/xeb.0000000000000054

Najm, A. A. K., Azfaralariff, A., Dyari, H. R. E., Othman, B. A., Shahid, M., Khalili, N., Law, D., Alwi, S. S. S., & Fazry, S. (2021). Anti-breast cancer synthetic peptides derived from the *Anabas testudineus* skin mucus fractions. *Scientific Reports*, *11*(1), Article 23182. https://doi.org/10.1038/s41598-021-02007-6

Narula, P., Kiruthika, S., Chowdhari, S., Vivekanandan, P., & Chugh, A. (2023). Inhibition of hepatitis B virus (HBV) by Tachyplesin, a marine antimicrobial cell-penetrating peptide. *Pharmaceutics*, *15*(2), Article 672. https://doi.org/10.3390/pharmaceutics15020672

Nyberg, F., Carlsson, A., & Hallberg, M. (2013). Casomorphins/Hemorphins. In A. J. Kastin (Ed.) *Handbook of Biologically Active Peptides* (pp. 1550–1555). Academi Press. https://doi.org/10.1016/b978-0-12-385095-9.00211-6

Oh, H. Y., Go, H. J., & Park, N. G. (2020). Identification and characterization of SaRpAMP, a 60S ribosomal protein L27-derived antimicrobial peptide from amur catfish, *Silurus asotus*. *Fish & Shellfish Immunology*, *106*, 480–490. https://doi.org/https://doi.org/10.1016 /j.fsi.2020.06.038

Okella, H., Ikiriza, H., Ochwo, S., Ajayi, C. O., Ndekezi, C., Nkamwesiga, J., Kaggwa, B., Aber, J., Mtewa, A. G., Koffi, T. K., Odongo, S., Vertommen, D., Kato, C. D., & Ogwang, P. E. (2021). Identification of antimicrobial peptides isolated from the skin mucus of *African Catfish*, *Clarias gariepinus* (Burchell, 1822). *Frontiers in Microbiology*, *12*, Article 794631. https://doi.org/10.3389/fmicb.2021.794631

Pelle, G. D., Perà, G., Belardinelli, M. C., Gerdol, M., Felli, M., Crognale, S., Scapigliati, G., Ceccacci, F., Buonocore, F., & Porcelli, F. (2020) Trematocine, a novel antimicrobial peptide from the antarctic fish *Trematomus bernacchii*: Identification and biological activity. *Antibiotics, 9*(2), Article 66. https://doi.org/10.3390/antibiotics9020066.

Peng, K. C., Lee, S. H., Hour, A. L., Pan, C. Y., Lee, L. H., & Chen, J. Y. (2012). Five different piscidins from *Nile tilapia*, *Oreochromis Niloticus*: Analysis of their expressions and biological functions. *PLoSOne*, *7*(11), Article e50263. https://doi.org/10.1371/journal.pone.0050263

Raju, V. S., Sarkar, P., Pachaiappan, R., Paray, B. A., Al-Sadoon, M. K., & Arockiaraj, J. (2020). Defense involvement of piscidin from striped murrel *Channa striatus* and its peptides CsRG12 and CsLC11 involvement in an antimicrobial and antibiofilm activity. *Fish & Shellfish Immunology, 99*, 368-378. https://doi.org/10.1016/j.fsi.2020.02.027

Rima, M., Fajloun, Z., Sabatier, J. M., Bechinger, B., & Naas, T. (2021). Antimicrobial peptides: A potent alternative to antibiotics. *Antibiotics*, *10*(9), Article 1095. https://doi.org/10.3390/antibiotics10091095

Rončević, T., Gerdol, M., Mardirossian, M., Maleš, M., Cvjetan, S., Benincasa, M., Maravić, A., Gajski, G., Krce, L., Aviani, I., Hrabar, J., Trumbić, Ž., Derks, M., Pallavicini, A., Weingarth, M., Zoranić, L., Tossi, A., & Mladineo, I. (2022). Anisaxins, helical antimicrobial peptides from marine parasites, kill resistant bacteria by lipid extraction and membrane disruption. *Acta Biomaterialia*, *146*, 131–144. https://doi.org/https://doi.org/10.1016/j.actbio. 2022.04.025

Russell, C. K., & Gregory, D. M. (2003). Evaluation of qualitative research studies. *Evidence-Based Nursing, 6*(2), 36-40. https://doi.org/10.1136/ebn.6.2.36

Semreen, M. H., El-Gamal, M. I., Abdin, S., Alkhazraji, H., Kamal, L., Hammad, S., El-Awady, F., Waleed, D., & Kourbaj, L. (2018). Recent updates of marine antimicrobial peptides. *Saudi Pharmaceutical Journal*, *26*(3), 396–409. https://doi.org/10.1016/j.jsps.2018.01.001

Sepulveda, J., & Wilson, M. (2019). *The use and abuse of antibiotics*. Institute for Global Health Sciences. https://globalhealthsciences.ucsf.edu/news/use-and-abuse-antibiotics

Subramaniam, G., Yew, X. Y., & Sivasamugham, L. A. (2020). Antibacterial activity of Cymbopogon citratus against clinically important bacteria. *South African Journal of Chemical Engineering, 34*, 26–30. https://doi.org/10.1016/j.sajce.2020.05.010

Tortorella, A., Leone, L., Lombardi, A., Pizzo, E., Bosso, A., Winter, R., Petraccone, L., Del Vecchio, P., & Oliva, R. (2023). The impact of N-glycosylation on the properties of the antimicrobial peptide LL-III. *Scientific Reports*, *13*(1), Article 3733. https://doi.org/10.1038/s41598-023-29984-0

Uddin, T. M., Chakraborty, A. J., Khusro, A., Zidan, B. R., Mitra, S., Emran, T. B., Dhama, K., Ripon, Md. K., Gajdács, M., Sahibzada, M. U., Hossain, M. J., & Koirala, N. (2021). Antibiotic resistance in microbes: History, mechanisms, therapeutic strategies and future prospects. *Journal of Infection and Public Health*, *14*(12), 1750–1766. https://doi.org/10.1016/j.jiph.2021.10.020

Vitali, A. (2018). Antimicrobial peptides derived from marine sponges. *American Journal of Clinical Microbiology and Antimicrobials, 1*(1), Article 1006.

Waghu, F. H., & Idicula-Thomas, S. (2019). Collection of antimicrobial peptides database and its derivatives: Applications and beyond. *Protein Science, 29*(1), 36-42 https://doi.org/10.1002/pro.3714

Walsh, D., & Downe, S. (2006). Appraising the quality of qualitative research. *Midwifery*, *22*(2), 108–119. https://doi.org/10.1016/j.midw.2005.05.004

Wang, S., Fan, L., Pan, H., Li, Y., Qiu, Y., & Lu, Y. (2023). Antimicrobial peptides from marine animals: Sources, structures, mechanisms and the potential for drug development. *Frontiers in Marine Science*, *9,* Article 1112595. https://doi.org/10.3389/fmars.2022.1112595

Wei, O. Y., Xavier, R., & Marimuthu, K. (2010). Screening of antibacterial activity of mucus extract of snakehead fish, Channa striatus (Bloch). *European Review for Medical and Pharmacological Sciences, 14*(8), 675–681.

Wu, Y., Wang, H., & Chu, P. K. (2023). Enhancing macrophages to combat intracellular bacteria. *The Innovation Life, 1*(2), 100027-100028. https://doi.org/10.59717/j.xinn-life.2023.100027

Xuan, J., Feng, W., Wang, J., Wang, R., Zhang, B., Bo, L., Chen, Z. S., Yang, H., & Sun, L. (2023). Antimicrobial peptides for combating drug-resistant bacterial infections. *Drug Resistance Updates*, *68*, Article 100954. https://doi.org/10.1016/j.drup.2023.100954

Ye, Z., Fu, L., Li, S., Chen, Z., Ouyang, J., Shang, X., Liu, Y., Gao, L., & Wang, Y. (2024). Synergistic collaboration between AMPs and non-direct antimicrobial cationic peptides. *Nature Communications, 15*(1), Article 7319. https://doi.org/10.1038/s41467-024-51730-x

Zasloff, M. (2002). Antimicrobial peptides of multicellular organisms. *Nature*, *415*(6870), 389–395. https://doi.org/10.1038/415389a

Zheng, X., Yuan, C., Zhang, Y., Zha, S., Mao, F., & Bao, Y. (2022). Prediction and characterization of a novel hemoglobin-derived mutant peptide (mTgHbP7) from *Tegillarca granosa*. *Fish & Shellfish Immunology, 125*, 84-89. https://doi.org/10.1016/j.fsi.2022.05.007