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Bioprospecting Aquatic Innate Immunity: Fish Mucus-Derived Compounds as Novel Human Therapeutics

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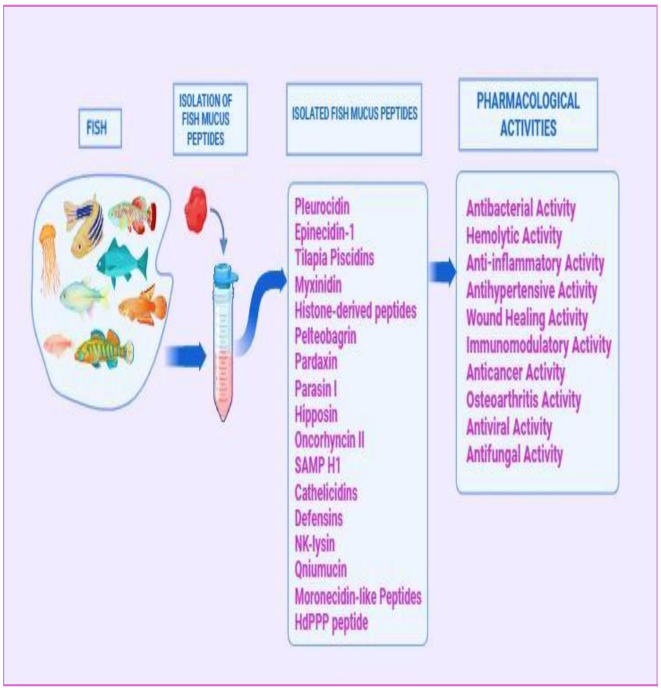
ABSTRACT
The increasing demand for novel therapeutic agents has led to a resurgence of interest in bioprospecting, particularly within the realm of aquatic organisms. Fish mucus, a viscous secretion that plays a crucial role in the innate immune system of fish, has emerged as a rich source of bioactive compounds with diverse pharmacological properties. This review explores the potential of fish mucus-derived peptides as innovative therapeutics for various human health challenges, including infections, inflammation, wound healing, and cancer. The antimicrobial properties of fish mucus peptides, including their efficacy against multidrug-resistant pathogens, highlight their promise as natural antibiotics. Additionally, their antifungal, antiviral, antiparasitic, and anti-inflammatory activities further underscore their therapeutic potential. The review also addresses the mechanisms of action of these peptides, their role in promoting wound healing, and their anticancer properties. Despite the promising applications, the exploration of fish mucus remains largely underutilized, necessitating further research to harness its full potential in drug discovery and development.
Keywords: N/A

GRAPHICAL ABSTRACT



INTRODUCTION:

The quest for novel therapeutic agents derived from natural sources has gained considerable attention in recent years, particularly in the context of bioprospecting. This approach seeks to identify and harness bioactive compounds from various organisms, with the aim of developing innovative treatments for a range of diseases[1]. Among the diverse biological materials explored, fish mucus has emerged as a promising reservoir of bioactive compounds with significant pharmacological potential[2–4]. Fish mucus, a viscous secretion produced by aquatic organisms[5,6], serves critical physiological functions, including protection against pathogens and environmental stressors[7–9]. Fish epidermal mucus represents a rich and underexplored biological compounds containing diverse bioactive, which necessitates a very effective and evolutionarily advanced natural immune system [7,10]. An essential part of this defense is the epidermal mucus layer, a complex vital secretion containing more number of bioactive molecules, including antimicrobial peptides, proteases, lectins, immunoglobulins, and mucins [4,8,9,11,12]. These molecules provide a physical and chemical barrier against pathogens, and they also control immune responses, wound healing, and communication in the aquatic environment for fish [4,8,13,14]. Fish mucus is a biomaterial whose scientific interest has grown in the last decade because of its broad-spectrum pharmacological activity reservoir of structurally diverse AMPs [3,15]. Fish are continuously exposed to large microbial loads compared to terrestrial organism [6,10] and this results in the evolution of powerful peptides against immunity, including piscidins, pleurocidin-1, myxinidin, epinecidin-1, histone-derived peptides . These peptides are highly antibacterial, antifungal, antiviral, anticancer, antioxidant, and immunomodulatory [16–19], and their action may be antipathogenic in most cases [4,15]. Multidrug-resistant pathogens have also increased interest in natural products like AMPs as the next generation of therapeutic agents [3,4,20]. Peptides produced by fish mucus are especially desirable in that they are usually cationic, amphipathic [3] and capable of disrupting microbial and fungal membranes [16,21] and interfering with protoplast regeneration [16]. The optimized fish mucus peptides can regulate inflammatory responses [22]. Although promising, fish mucus is still a massively untapped biological source, and numerous species have not been used to get new peptides or bioactivities [3,15]. The bioprospecting activity in this field is not only supporting the process of drug discovery but also corresponds to sustainable use of marine resources, particularly those obtained through aquaculture by-products or non-lethal mucus samples [3,23]. With the increasing demand of effective, safe and environmentally friendly therapeutics, research on fish mucus-derived peptides is a timely and interesting frontier in pharmaceutical studies. This discussion review focuses on the pharmacological spectrum, action mechanisms of fish mucus peptides, and therapeutic opportunities, outlining their prospects of application in controlling infections, wound healing, inflammation and cancer treatment issues in the world.

Therapeutic Potential of Fish Mucus–Derived Bioactive Molecules

Antimicrobial Activities

Fish skin mucus contains various antibacterial substances, including antimicrobial peptides (AMPs) and lysozymes, which provide a primary defense against pathogenic microbes, helping to protect fish from diseases and infections [24]. Fish-derived antimicrobial peptides (AMPs) demonstrate a wide range of inhibitory effects against various pathogens, including viruses, fungi, bacteria, and parasites. This broad-spectrum activity positions them as essential components of the innate immune systems in numerous fish species [25] . Their effectiveness in combating different infections underscores their value as natural antibiotics [26,27] Hence, the potential applications of fish-derived AMPs extend beyond aquaculture; they can function as antibacterial, antiviral, anti-parasitic, and antifungal agents, as well as serve as vaccine adjuvants and components of inactivated vaccines. This versatility highlights their practical utility in addressing antibiotic resistance and enhancing immune responses [25]. Furthermore, the analysis indicates that the antimicrobial activity of these peptides is influenced by their amino acid composition, particularly the presence of basic and aromatic amino acids, which are crucial for their effectiveness against pathogens [19]. Fish AMPs—including families such as piscidins, pleurocidins, epinecidins, myxinidin, pardaxins, and histone-derived peptides are typically small, cationic, amphipathic molecules capable of disrupting microbial membranes, modulating immune responses, and in some cases inducing apoptosis in infected or abnormal host cells [18,28]. Their ability to target both Gram-positive and Gram-negative bacteria, as well as fungi, viruses, and protozoa, underscores their multifunctional therapeutic potential [16,17]. Several AMPs derived from fish mucus have demonstrated exceptional potency against multidrug-resistant clinical pathogens, highlighting their relevance in the context of rising antimicrobial resistance [3,4].The sustained interest in these natural compounds is further amplified by the global challenge of multidrug-resistant pathogens, positioning fish mucus peptides as promising candidates for next-generation antibacterial agents [3,4].

Antibacterial Activity

Fish mucus-derived antimicrobial peptides have gained significant scientific attention due to their potent antimicrobial properties, broad-spectrum activity, and low likelihood of inducing microbial resistance [3,4,15,20]. The antibacterial efficacy of fish mucus has been extensively documented, with numerous studies demonstrating its potent inhibitory effects against a wide range of bacterial pathogens [29 30]. Antibacterial peptides, also known as host defense peptides, are a crucial component of the innate immune system in fish. They are small, cationic (positively charged) molecules that play a vital role as a first line of defense against a wide array of pathogens in their aquatic environment [31,32]. Fish rely heavily on this innate immunity to survive in microbe-rich waters [33].Among various fish species, *Clarias batrachus* epidermal mucus extracts have demonstrated strong antimicrobial activity, showing high inhibitory effects against a range of pathogens including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Escherichia coli*, even suggesting efficacy against antibiotic-resistant superbugs like NDM through molecular docking [34,35]. This broad-spectrum action aligns with findings in other fish, such as *Monopterus cuchia* which exhibits antimicrobial activity comparable to ampicillin against *E. coli* and *S. aureus* [36], and the topmouth culter, whose derived AMPs show anti-infective effects against drug-resistant bacteria and synergistic benefits with antibiotics [37]. Specifically, the antimicrobial activity of mucus from economically important freshwater fish species, including *Oreochromis niloticus* (tilapia), *Clarias batrachus* (catfish), and *Channa striata* (snakehead fish), were investigated against pathogens. The antimicrobial activity of combined fish mucus has been observed against multi-drug resistant pathogens such as MBL-*Pseudomonas aeruginosa*, ESBL-*Escherichia coli*, and Methicillin-Resistant *Staphylococcus aureus*, underscoring its potential in combating critical antibiotic resistance [34].

Table 1: Fish epidermal mucus peptides that have Antibacterial property

Peptide Name	Source Fish	Antimicrobial Spectrum	Reference
Epinecidin-1	orange-spotted grouper (*Epinephelus coioides*)	Active against Gram-positive and Gram-negative bacteria, including multidrug-resistant strains	38,39
Pleurocidin	winter flounder (*Pleuronectes americanus*)	Active against Gram-positive and Gram -negative bacteria, including MRD	21,40
Tilapia Piscidins	(Tilapia species, e.g., *Oreochromis niloticus*)	Active against Gram-positive and Gram-negative bacteria, including MDR strains. It also showed anticancer and antiviral activity	41
Pleurocidin	*Pleuronectes americanus*	Active against *Candida* species and marine fungi. Also exhibits immunomodulatory and cytotoxic effects against cancer cells	41–45
Epinecidin-1	Grouper (*Epinephelus coioides*)	Broad-spectrum antimicrobial activity (antibacterial, antifungal), inhibits proliferation and induces apoptosis in human leukemia cells	22,38,46
Pelteobagrin	*Pelteobagrus fulvidraco*	Amphipathic\alpha-helical peptide; broad-spectrum antibacterial activity without hemolytic effects	32,47
Pardaxin	*Pardachirus marmoratus*	Broad-spectrum Antibacterial toxin peptide; also has antitumor activity	4,39,48
Piscidin 1	Hybrid striped bass (*Morone saxatilis* x *M. chrysops*)	Broad-spectrum AMP; cytotoxic to osteosarcoma, lung, and ovarian cancer cells	22
Myxinidin	*Myxine glutinosa*	Cationic 12-AA peptide; Broad-spectrum antibacterial	49
Hipposin	*Hippoglossus hippoglossus*	Broad-spectrum activity, inhibits *Enterococcus fecalis*, *Listeria ivanovii*, and *Staphylococcus epidermis* by degrading microbial walls	4,50
Parasin I	*Parasilurus asotus*	Very Broad-spectrum Antibacterial	51
Histone H2A peptide	*Oncorhynchus mykiss*	Broad-spectrum Antibacterial; also shows anticancer activity against lung and laryngeal cells	4,41,52
SAMP H1	*Salmo salar*	Broad-spectrum Antimicrobial	53
Oncorhyncin II	*Oncorhynchus mykiss*	Derived from Histone H1; Broad-spectrum antibacterial	50
Hepcidin-like peptide	*Takifugu pardalis*	Novel 23 amino acid peptide that inhibits the growth of Gram-negative and Gram-positive microbes	4
Cysteine-rich AMPs (cathelicidins, defensins)	Various fish species	Effectively inhibit the growth of Gram-negative and Gram-positive bacteria	4

Peptides from *Neogobius fluviatilis pallasi*	*Neogobius fluviatilis pallasi*	Demonstrated bacterial inhibition activity against *Staphylococcus aureus* and *Bacillus subtilis*	54

Antifungal Activity

The antifungal properties of fish mucus have also been well-documented, with various studies highlighting its effectiveness against pathogenic fungi such as *Candida albicans* [55].This capacity underscores the potential for developing novel antifungal agents from fish mucus, particularly given the rising concern of drug-resistant fungal infections [55].Antimicrobial peptides from fish mucus, such as Pleurocidin, Myxinidin, and Piscidin 2, have demonstrated potent activity against fungi [3,21,22,55]. These peptides likely exert their antifungal effects through mechanisms that involve disrupting the fungal cell membrane, inhibiting the germination of conidia (asexual fungal spores), and interfering with chitin synthesis, a vital component of the fungal cell wall [22,56]. studies have shown that mucus extracts from *Oreochromis niloticus* exhibit significant antifungal activity against *Candida albicans*, demonstrating considerable zones of inhibition [55]. This antifungal capacity underscores the potential for developing novel antifungal agents from fish mucus, particularly given the rising concern of drug- resistant fungal infections [55].

Table 2: Fish epidermal mucus peptides and its Antifungal property

Peptide Name	Source Fish	Notes / Function	Reference
Piscidin 2	Hybrid striped bass (*Morone saxatilis* x *M. chrysops*)	Active against *Candida albicans*, *Malassezia furfur*, *Trichosporon beigelii*, and *Saprolegnia*. Produced by mast cells, effective against human pathogenic fungi.	22,57,58
Myxinidin	Hagfish(*Myxine glutinosa*)	Fungicidal effect on *Candida albicans*, 2-16 times more active than pleurocidin. Low hemolytic activity.	22,49
Pleurocidin	Winter flounder (*Pleuronectes americanus*)	Potent antifungal activity with low hemolytic activity.	59
Hepcidin AMP (synthetic)	Hybrid striped bass	Antifungal influence against *Aspergillus niger*.	58
AS-hepcidin-6	*Acanthopagrus schlegelii*	Potent antifungal activity against *Candida albicans*.	58
PChepc	*Pseudosciaena crocea*	Antifungal activity against *Fusarium graminearum*, *Candida albicans*, and *F. solani*.	58
HLP-1, HLP-2	*Ictalurus punctatus*	Proven antifungal activities against *Saprolegnia parasitica*.	58
Parasin I	Catfish	Inhibits *Candida albicans*.	22
Pelteobagrin	Catfish	Inhibits *Candida albicans*.	22
SaRpAMP	Catfish	Inhibits *Candida albicans*.	22
EcPis-2L, EcPis-4L	*Epinephelus coioides*	Homologs of piscidin, have inhibitory effects on fungi.	22

Antiviral Properties

Fish mucus peptides exhibit antiviral properties, making them promising candidates for new antiviral agents [60,61]. These peptides play a dual role in antiviral defense, acting directly on the virion and influencing the host cell [61].While information specifically on fish *mucus* peptides with antiviral activity is still considered scarce [3], broader fish-derived AMPs have shown effectiveness. Overall, fish AMPs are recognized for their broad-spectrum activity against various pathogens, including viruses [31,62,63]. The ongoing research aims to further elucidate the mechanisms of action and identify more such compounds for potential application in aquaculture and human health [61]. A peptide from the methanol skin mucus extract of *Cirrhinus mrigala* demonstrated potential antiviral activity against Infectious Pancreatic Necrosis Virus (IPNV) and Infectious Salmon Anemia Virus (ISAV) through protein-peptide docking analysis, indicating good interactions with viral particles. The modeled peptide exhibited high similarity to Arminin-1 from Cnidaria animals, suggesting that it may possess antimicrobial properties that could be leveraged in the development of novel peptide candidates for controlling viral diseases in aquaculture [64]. Antiviral peptides (AVPs) derived from fish mucus, such as Pa-MAP (multiple active peptides from *Pleuronectes americanus*), have demonstrated significant antiviral activity, particularly against herpes simplex viruses (HSVs). This particular peptide was originally isolated from the skin of the polar fish *P. americanus*.[65]

Table 3: Fish epidermal mucus peptides and its antiviral activity

Peptide Name / Type	Source	Activity / Key Findings	Reference
Piscidins (e.g., Tilapia Piscidins)	Various fish (e.g., *Oreochromis niloticus*)	Have shown antiviral activity, including against nervous necrosis virus antiviral activity against various viruses, such as Pseudorabies virus, and possess broad-spectrum antiviral properties	18,41,62,66,67
Pleurocidin	*Limanda limanda*	Studied for activity against Viral Hemorrhagic Septicemia Virus	61
Hepcidin	Tilapia (*Oreochromis mossambicus*), flounder (*Paralichthys olivaceus*)	Can agglutinate NNV, inhibiting cell contact, and have shown antiviral activity against HIRRV *In vitro*	66,68
NK-lysin	Flounder (*Paralichthys olivaceus*)	Demonstrated antiviral activity against HIRRV *In vitro*	68

Antiparasitic activity:

The application-oriented properties of fish AMPs, emphasizing their role not only as antibacterial and antiviral agents but also in combating parasitic infections, thereby offering a promising alternative to traditional antiparasitic treatments [69]. The research study identified specific synthetic peptides, namely 5065 and 5070, that effectively inhibit the growth of the parasitic copepod *Caligus rogercresseyi* during its copepodite stage, suggesting their potential as antiparasitic agents. Furthermore, the analysis of these peptides indicated that their biological functions, including antiparasitic activity, are influenced by their amino acid composition. In particular, the presence of basic and aromatic amino acids is linked to enhanced antimicrobial and antiparasitic properties [19]. The wormicidal effects of mucous substances from 9 species of freshwater fishes on *Clonorchis sinensis*, a parasitic flatworm, was reported in research. Different species exhibited varying levels of effectiveness against cercaria, metacercaria, and adult stages of the parasite, indicating potential antiparasitic properties. The time required for the wormicidal effect varied significantly among the fish species, with the most effective being *C. carassius* (crusian carp), which took 14 minutes to affect cercaria [70].

Anti-inflammatory Properties

The unique composition of fish mucosal secretions, influenced by various endogenous and exogenous factors, may provide insights into the identification of new therapeutic agents with anti- inflammatory properties [71]. The mucus-secreting glands derived from the shell-shucking waste of Haliotis discus hannai exhibited significant anti-inflammatory properties by reducing nitric oxide (NO) production and inhibiting the expression of inflammatory mediators, including the cytokines TNF-α, IL-1β, and IL-6, as well as the enzymes iNOS and COX-2 in RAW 264.7 mouse macrophage cells. Furthermore, the presence of by-products from *H. discus* hannai mucosubstance (AM) not only curtailed the overexpression of these inflammatory mediators but also enhanced the expression of the anti-inflammatory response mediator HO-1. This indicates a dual mechanism of action, wherein inflammation is reduced while anti-inflammatory pathways are simultaneously promoted [72]. Epinecidin-1 peptide, found in fish like the orange-spotted grouper (*Epinephelus coioides*), can modulate immune responses and influence interleukin expression, which is indicative of its anti- inflammatory potential [22,38,46,73–77]. It enhances macrophage activation and promotes tissue regeneration [16,38,78]. Some piscidins have also been identified to modulate inflammatory markers and cytokines [22,73–77].

Table 4: Fish epidermal mucus peptides with Anti-inflammatory property

Peptide Name / Type	Source	Method of Anti-inflammation	Reference
Epinecidin-1	Orange-spotted grouper (*Epinephelus coioides*)	Modulates immune responses, influences interleukin expression, enhances macrophage activation, promotes tissue regeneration.	22,38,46,73–77
Piscidins	Various fish	Modulate inflammatory markers and cytokines.	22,73–77
Histone-derived	Teleost fish	Immunomodulatory capabilities, regulating immune	19
peptides		responses.	

Antioxidant Activity

Fish mucus peptides have demonstrated notable antioxidant properties, which contribute to their overall protective role. Studies have shown that these peptides can exhibit scavenging activity against various free radicals, such as DPPH and ABTS radicals [54,71]. For instance, epidermal exudates from the Caspian sand goby (*Neogobius fluviatilis pallasi*) and body mucus from *Halobatrachus didactylus* have been found to possess significant antioxidant potential [54,71,79]. Mackerel mucus components also demonstrate antioxidant activity, suggesting their potential use in cosmetic applications [80]. Histone-derived peptides identified in fish mucus are also noted for their potential antioxidant properties [19]. These findings highlight the potential of fish mucus peptides as a source of natural antioxidants for various applications.

Table 5: Fish epidermal mucus peptides having Antioxidant property

Peptide Name / Type	Source	Method of Antioxidant Action	Reference
Epidermal exudates	Caspian sand goby (*Neogobius fluviatilis pallasi*)	Scavenging activity against various free radicals, such as DPPH and ABTS radicals; significant antioxidant potential	54,71
Body mucus	*Halobatrachus didactylus*	Significant antioxidant potential; scavenging activity against various free radicals	71,79
Mucus components	Mackerel	Demonstrated antioxidant activity through suppressing oxidative stress	80
Histone-derived peptides	Teleost fish	Potential antioxidant properties by scavenging free radicals	19

Anti-Osteoarthritic activity:

Qniumucinan, which is a type of jellyfish mucin (extracted from species like *Aurelia aurita* and *Stomolophus nomurai*), has been investigated for its potential to alleviate osteoarthritis symptoms. Preclinical studies, particularly in rabbit models of osteoarthritis, have indicated that intra-articular injections of qniumucin may have disease-modifying effects on articular cartilage degeneration, especially when combined with hyaluronic acid. This combination demonstrated a significant reduction in cartilage degeneration [81,82]. Marine-derived Peptides for Osteoarthritis are emerging as significant origins for bioactive peptides that can positively influence osteoarthritis [83,84]. No clinical trials identified yet.

Hemolytic activity:

Hemolytic activity refers to the capacity of certain substances to induce the lysis, or destruction, of red blood cells. In the realm of bioprospecting fish mucus-derived peptides for therapeutic applications, hemolytic activity is generally considered an undesirable characteristic or a "defect" that can impede their clinical use [22]. Many antimicrobial peptides found in fish mucus are amphipathic, meaning they possess both hydrophobic and hydrophilic regions. This amphipathic nature allows them to interact with and disrupt cell membranes, including those of red blood cells, acting in a detergent-like manner [4].Furthermore, a review on fish AMPs highlights that "the defects of natural fish AMPs, such as their high hemolytic activity and low stability, hinder their application" [22]. Mucus extracts from the giant mudskipper

(*Periophthalmodon schlosseri*) have demonstrated hemolytic effects against both chicken and human red blood cells [85]. Similarly, mucus from *M. armatus* exhibited hemolytic activity against sheep and cow blood cells [85]. While some moronecidin-

like peptides from Antarctic fishes have shown lower hemolytic activity, this still implies that moronecidin itself can have such effects [86]. The presence of high hemolytic activity is a significant challenge for developing these promising fish antimicrobial peptides into safe and effective therapeutic agents [22].

Table 6: Hemolytic activity of fish epidermal mucus

Peptide/Extract	Source Fish Species	Hemolytic Activity Details	Reference
Mucus Extracts	*Periophthalmodon schlosseri*	Exhibited hemolytic activities against both chicken and human red blood cells, with maximum activity observed for dichloromethane extracts	85
Mucus Extracts	*M. armatus*	Exhibited hemolytic activity against sheep and cow blood cells	85,87
Amphipathic Helical Peptides	Various Fish Species	Mucus from some fish contains these peptides, which can act as detergents, binding with anionic phospholipids and leading to the lysis of cells	4
Moronecidin-like Peptides	*Notothenia coriiceps* and *Parachaenichthys charcoti*	While these specific peptides exhibited *lower* hemolytic activity, their comparison implies that moronecidin (or similar structures) can possess hemolytic effects	86

Antihypertensive Activity

Fish peptides have been identified as potent inhibitors of the angiotensin-converting enzyme (ACE), which plays a crucial role in blood pressure regulation. This activity is particularly noted in peptides derived from fish skin and muscle hydrolysates[10,88]. ACE plays a crucial role in blood pressure regulation by converting angiotensin I into the vasoconstrictor angiotensin II, which narrows blood vessels, and by inactivating bradykinin, a peptide that helps relax blood vessels [10,89]. By inhibiting ACE, these peptides can help prevent the rise in blood pressure, offering a natural and promising approach to managing hypertension [89,90]. The mechanism of ACE inhibition by these marine peptides often involves competitive binding to ACE's active site, interfering with its conformational changes, and preventing the binding of its natural substrates [91]. The structure of these peptides, particularly the presence of hydrophobic amino acids, is closely related to their ACE- inhibitory effects, as it improves their solubility in lipid-based conditions and enhances their absorption in the intestine, allowing them to reach target cells [92]. The novel peptide Pro-Thr-His-Ile- Lys-Trp-Gly-Asp exhibits excellent antihypertensive activity, making it a promising candidate for managing high blood pressure. This peptide demonstrates significant ACE inhibitory activity, which is crucial for its effectiveness as an antihypertensive substance, along with low toxicity and good stability.[93]

Table 7: Antihypertensive activity of fish epidermal mucus

Peptide Name / Type	Source	Activity / Key Findings	Reference
HdPPP peptide	*Halobatrachus didactylus* (toadfish) body	Comparable antihypertensive activity to other fish peptides, rich in proline, similar binding characteristics to the synthetic drug Captopril	79
	mucus		

Wound Healing Activity

Fish mucus has gained significant recognition for its remarkable wound healing capabilities, a capacity particularly evident in fish species that exhibit superior regenerative abilities compared to mammals [94]. The capacity for wound healing is critical for organismal survival, and fish, particularly teleosts, exhibit remarkable regenerative capabilities that surpass those observed in mammals [94]. Recent studies have underscored the potent wound-healing efficacy of fish mucus, particularly from species like *Pangasianodon hypophthalmus*, demonstrating significant applications in both *In vitro* cellular proliferation assays and *in vivo* wound closure models [95]. Approximate Proportion: 10% Enhances macrophage activation and promotes tissue regeneration [16].Arginine in fish mucus acts as a precursor for nitric oxide, which plays a crucial role in immune response, angiogenesis, epithelialization, and tissue formation during wound healing .The NO generated from arginine in fish mucus plays a crucial role in several key pharmacological activities, primarily contributing to effective wound healing and immune regulation Studies have shown that mucus from snakehead fish can accelerate wound healing and demonstrate strong antibacterial activity against pathogens like *Escherichia* *coli*, suggesting its utility in developing advanced wound care products [13]. *Pangasianodon hypophthalmus* mucus has also been shown to promote significant cell viability, indicating its cytocompatibility and ability to support tissue repair with minimal toxicity [95].Components such as dermatan, keratan, and chondroitin sulfates found in fish mucus are believed to enhance collagen fiber organization and wound contraction, leading to more efficient tissue repair [96]. Specific peptides like Epinecidin-1 have been noted for their role in enhancing macrophage activation and promoting tissue regeneration [16]. The broad-spectrum activity of fish mucus AMPs also positions them as promising candidates for dermatological therapies [97].While fish mucus extracts broadly promote wound healing (e.g., via cell proliferation and migration [13,95]), the number of named peptides with direct evidence remains limited. Other piscidin family members (e.g., pardaxin, pleurocidin) from mucus show potential via multifunctional activities [71].

Table 8: Fish epidermal mucus and its wound healing property

Peptide Name	Source Fish/Species	Wound Healing Evidence	Reference
Epinecidin-1	Orange-spotted grouper (*Epinephelus coioides*)	Promotes epithelial proliferation, cell cycle progression, migration via extracellular matrix regulation; accelerates complete regeneration in MRSA-infected swine burn wounds.	38,78
Tilapia Piscidin2-5 & TP2-6	Tilapia (*Oreochromis* spp.)	Investigated for wound healing potential, with effects on cells involved in repair (e.g., similar to other AMPs modulating immune response and proliferation)	98

Anticancer Potential

The anticancer property refers to the ability of these substances, particularly antimicrobial peptides, to selectively inhibit the growth of cancer cells, induce programmed cell death (apoptosis), and modulate the immune response, often with reduced toxicity to healthy tissues compared to conventional chemotherapy .Peptides like are being investigated for their selective cytotoxic effects on cancer cells, such as osteosarcoma, by inducing mitochondrial dysfunction and apoptosis . is known to inhibit proliferation and induce apoptosis in human leukemia cells and stimulates interleukin expression. and its derivatives are being explored for their anticancer capabilities. Additionally, and demonstrate

inhibitory activities against various tumor cell lines. AMPs are promising alternatives to traditional cancer treatments due to their selectivity for cancer cells and reduced toxicity to healthy tissues actively inhibit the growth of cancer cells, induce programmed cell death (apoptosis), and modulate the immune response, often with reduced toxicity to healthy tissues compared to conventional chemotherapy [22,43].Peptides like Piscidin 1 are being investigated for their selective cytotoxic effects on cancer cells, such as osteosarcoma, by inducing mitochondrial dysfunction and apoptosis [22]. Epinecidin-1 is known to inhibit the proliferation and induce apoptosis in human leukemia cells and stimulates interleukin expression [22]. Pleurocidin and its derivatives are being explored for their anticancer capabilities [99]. Additionally, hepcidins and histone-derived peptides demonstrate inhibitory activities against various tumor cell lines [100]. AMPs are promising alternatives to traditional cancer treatments due to their selectivity for cancer cells and reduced toxicity to healthy tissues [43].A scoping review on fish-derived hepcidins highlights potential anticancer and antimicrobial use, but not clinical trials [101].

Table 9: Anticancer activity of fish mucus peptides

Peptide	Source Fish	Cancer Cell Lines/Activity	Mechanism of Action	Reference
Piscidin 1	Hybrid striped bass (*Morone saxatilis x M. chrysops*)	Osteosarcoma, lung, and ovarian cancer cells	Cytotoxic; induces mitochondrial dysfunction, alters mitochondrial active oxygen species, reduces mitochondrial transmembrane potential, and decreases mitochondrial antioxidant manganese superoxide dismutase, leading to apoptosis	22

Epinecidin-1	Grouper (*Epinephelus coioides*)	Human leukemia U937 cells, HT1080 fibrosarcoma cells	Inhibits proliferation, induces apoptosis, interacts with anionic phospholipids in bacterial (and likely cancer) cell membranes, causing cell lysis. It increases tumor necrosis factor-α, interleukins-10, IFN-γ, p53, IL-15, and IL-6, and increases the ADP/ATP ratio, indicating mitochondrial dysfunction	22,38,46
Pleurocidin	Winter flounder (*Pleuronectes americanus*)	Human breast cancer cells, mammalian carcinoma cells, A549 human lung adenocarcinoma cells (as Pleurocidin-amide, Ple-a), leukemia Jurkat cells (as a pleurocidin-like peptide from *Poecilia Mexicana*)	Cytotoxic; Pleurocidin-amide inhibits autophagy and induces apoptosis in A549 cells	41,43–45
Tilapia Piscidin 4	*Oreochromis niloticus*	Glioblastoma cell lines (U87MG, U251)	disruption of cellular infrastructure and energy metabolism	41
Histone H2A Peptide	Various fish sources (e.g., *Oncorhynchus mykiss*)	Lung and laryngeal cells	accumulate in the nucleus to trigger mitochondria-dependent apoptosis	41
Pardaxin	Red sea flatfish (*Pardachirus marmoratus*)	MN-11 cells	apoptosis by targeting the endoplasmic reticulum (ER) and mitochondria	48
TH1-5, TH2-3	Tilapia (*Oreochromis mossambicus*)	Human cervix adenocarcinoma cells, human hepatocellular carcinoma cells, human fibrosarcoma cells	targeting the cell membrane and inducing apoptosis.	48,102
Chrysophsin-1	Red sea bream	Antitumor activities [48]	disrupting cancer cell membranes	48

Thrombogenic Activity

Fish skin mucus exhibits thrombogenic activity, meaning it has the capacity to stimulate blood coagulation. This is attributed to components within the mucus that can reduce blood clotting time. Research indicates that fish skin mucus contains factors that promote blood coagulation, including proteins that are functionally homologous to thromboplastin (clotting factor III) and prothromboplastin (clotting factor XI). These properties suggest the presence of thrombokinase and kinins, which facilitate rapid blood coagulation in response to injury in fish.

Although direct amino acid sequence homology with human thromboplastin and prothromboplastin have not been definitively established, the ability of fish mucus to stimulate coagulation and the interaction of its fractions with relevant antibodies point to a functional resemblance. The presence of proteins in the 25–35 kDa range is thought to correspond to these coagulation-promoting factors. These findings suggest that fish mucus peptides could be a promising source for developing pharmacological preparations aimed at stopping or preventing bleeding [103].

Immunomodulatory Activity

Fish epidermal mucus plays a crucial role in the innate immune system of fish, and its peptides contribute significantly to immunomodulatory activities. The mucus contains a diverse array of immune-related factors, including lectins, lysozyme, immunoglobulins, complement proteins, and C- reactive protein, all of which work in concert to provide a robust defense against pathogens [12,104]. Teleost fish peptides, including HDPs, have been identified for their immunomodulatory capabilities, suggesting their ability to regulate immune responses [19]. This function is vital for protecting fish in their microbe-rich aquatic environment and offers avenues for developing novel immunomodulatory agents in human health [11,97].

Table 10: Fish epidermal mucus peptides with Immunomodulatory property

Peptide/Extract	Source Fish Species	Activity Details	Reference
Teleost fish peptides (including HDPs)	Teleost fish	Possess immunomodulatory capabilities; regulate immune responses; contribute to a robust defense against pathogens; vital for protecting fish in microbe-	11,19,97
		rich environments; offer avenues for developing novel immunomodulatory agents in human health.	
Lectins	Fish epidermal mucus	Contribute to a robust defense against pathogens.	12,104
Lysozyme	Fish epidermal mucus	Contribute to a robust defense against pathogens.	12,104
Immunoglobulins	Fish epidermal mucus	Contribute to a robust defense against pathogens.	12,104
Complement proteins	Fish epidermal mucus	Contribute to a robust defense against pathogens.	12,104
C-reactive protein	Fish epidermal mucus	Contribute to a robust defense against pathogens.	12,104

CONCLUSION

Fish mucus represents a largely untapped reservoir of bioactive compounds with significant therapeutic potential. The diverse pharmacological activities of fish mucus-derived peptides, including their antimicrobial, antifungal, antiviral, antiparasitic, anti-inflammatory, and anticancer properties, position them as promising candidates for the development of next-generation therapeutics. The ongoing challenges posed by antibiotic resistance and the need for safe, effective, and environmentally friendly treatments further amplify the relevance of fish mucus in pharmaceutical research. Future studies should focus on the systematic exploration of various fish species and their mucus components, emphasizing sustainable practices and the potential for aquaculture by-products. By advancing our understanding of the mechanisms underlying the therapeutic effects of fish mucus peptides, we can pave the way for innovative treatments that address critical health issues in both humans and animals.

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