Lai et al. *Zool. Res.* 2026, 47(1): 233–249
https://doi.org/10.24272/j.issn.2095-8137.2025.509
https://cstr.cn/32248.14.zr.2025.509

ZR | Zoological Research

Review Open Access

Peptides derived from exocrine secretions of venomous animals used as traditional Chinese “worm” medicines

Shian Lai[1,#], Jinwei Chai[2,#], Yongtao Luo[2], Lei Luo[3,*], Xueqing Xu[2,*]

[1] *Department of Life Sciences*, *Graduate School of Arts and Sciences*, *University of Tokyo*, *Tokyo* 153-8902, *Japan*

[2] *NMPA Key Laboratory for Research and Evaluation of Drug Metabolism*, *Guangdong Provincial Key Laboratory of New Drug Screening*, *School of Pharmaceutical Sciences*, *Southern Medical University*, *Guangzhou*, *Guangdong* 510515, *China*

[3] *State Key Laboratory of Genetic Evolution and Animal Models*, *Key Laboratory of Bioactive Peptides of Yunnan Province*, *Kunming Institute of Zoology*, *Chinese Academy of Sciences*, *Kunming*, *Yunnan* 650107, *China*

ABSTRACT

The term “worm medicines” (Chong Yao) in Traditional Chinese Medicine encompasses a diverse category of small animal-derived therapeutics, including arthropods, amphibians, and reptiles, rather than strictly vermiform organisms. Many of these animals, such as scorpions, centipedes, toads, and horseflies, are toxic, and have been employed in clinical practice for centuries, despite limited understanding of their active compounds and underlying modes of action. Among the bioactive constituents extracted from these taxa, peptides represent a particularly promising class, with over 2 000 identified to date. These peptides are primarily secreted from specialized exocrine glands, including venom, salivary, and cutaneous glands, and are characterized by high structural diversity and target specificity. Their potent modulatory effects on the nervous, cardiovascular, and immune systems make them excellent candidates for drug discovery and development. This review examines peptide-based compounds derived from the exocrine secretions of venomous and poisonous taxa historically employed in traditional Chinese **“**worm**”** medicines. Emphasis is placed on their biological origins, structural features, and pharmacological activities, highlighting their significant potential as a rich and largely untapped resource for modern therapeutic discovery.

Keywords: Poisonous worms; Pharmacological constituents; Mechanisms; Traditional Chinese "worm" medicines; Peptides; Physiological elements; Drug discovery

INTRODUCTION

Across evolutionary timescales, animals have developed an extraordinary arsenal of chemical defenses and offensive agents to navigate a wide range of ecological challenges, including microbial invasion, parasitism, predation, and abiotic stress. Among these adaptations, exocrine secretions from specialized glands such as venom, skin, and salivary glands have independently emerged in multiple lineages, representing a striking example of convergent evolution. Current estimates suggest that over 220 000 venomous animal species exist worldwide, constituting approximately 15% of global animal biodiversity and distributed across nearly all major clades (Herzig, 2021; Lent & Dickinson, 1984). The striking biochemical diversity and potent bioactivity of these secretions have long captivated human interest, leading to their exploitation in traditional medicine for thousands of years (Herzig, 2021). Ancient civilizations across Asia, Africa, and the Mediterranean—particularly those in China, Egypt, India, Greece, and the Arab world—documented the therapeutic utility of toxic organisms despite recognized risks (Goyffon & Tournier, 2014). Within the framework of Traditional Chinese Medicine (TCM), venomous and poisonous taxa have long been utilized for their therapeutic potential, notably within the category of “worm” medicines (Chong Yao). Contrary to a literal interpretation, this term encompasses a taxonomically diverse assemblage of small animals, including insects (e.g., wasp, horsefly), mollusks (e.g., leeches), arthropods (e.g., scorpions, centipedes, and spiders), and small reptiles (e.g., frogs, toads, and snakes) (Jiang et al., 2014; Liu et al., 2024b; Luo et al., 2023; Shi et al., 2017). These organisms have been utilized for their exocrine-derived bioactive compounds and therapeutic agents in treating a range of human disorders (Figure 1).

Received: 27 November 2025; Accepted: 28 December 2025; Online: 29 December 2025

Foundation items: This work was supported by the Key Research and Development Program of Guangzhou Science and Technology Plan Project (2024B03J0011), National Natural Science Foundation of China (32522015, 32570586, 32370538), National Key Research and Development Program of China (2023YFF1304900), and Yunnan Province Grant (2021000097, 202402AA310010, 202403AC100010)

[#]Authors contributed equally to this work

*Corresponding authors, E-mail: luolei@mail.kiz.ac.cn; xu2003@smu.edu.cn

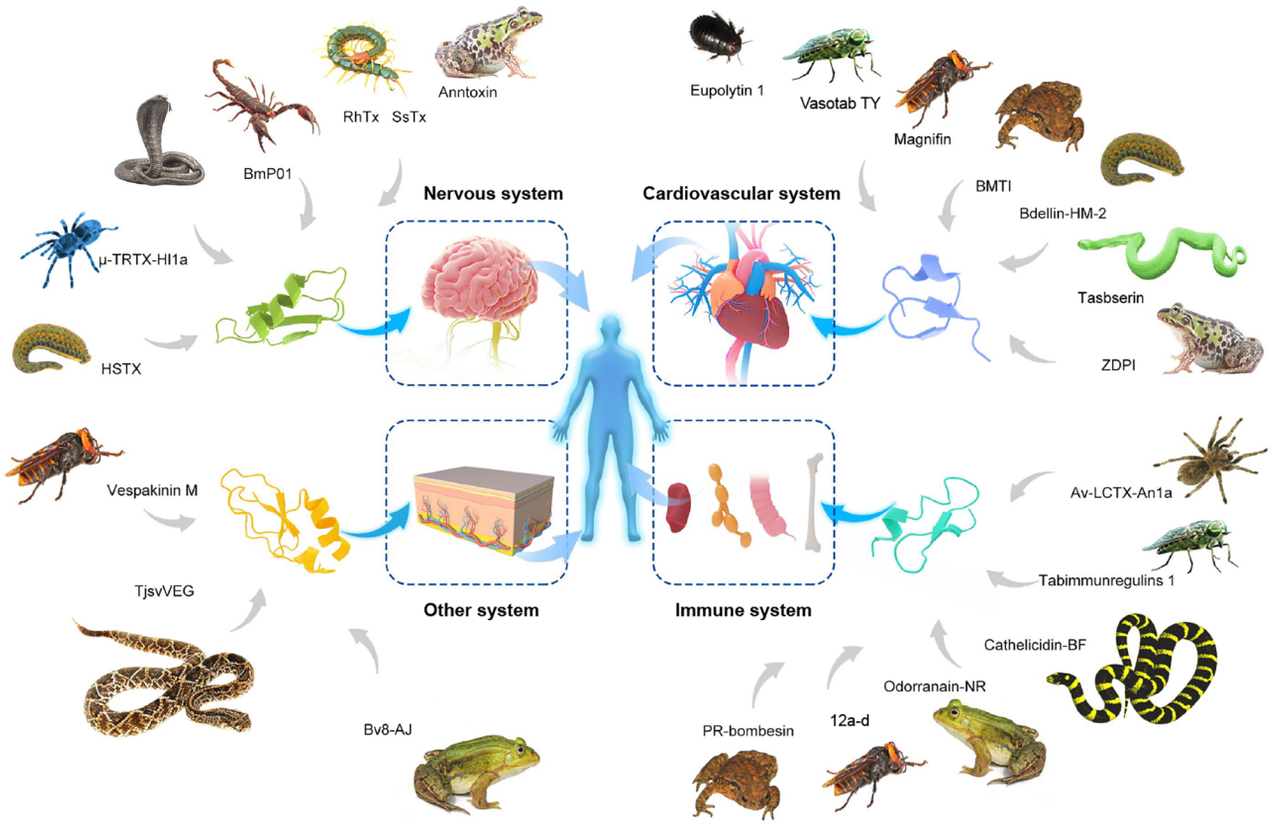

Figure 1 Representative traditional Chinese "worm" medicines and peptide-based products with activity across cardiovascular, immune, nervous, and other physiological systems

Gray arrows indicate bioactive peptides secreted by traditional Chinese "worms". Dark blue arrows indicate downstream therapeutic products acting on the cardiovascular, immune, nervous, and other systems. Light blue arrows indicate affected human physiological systems.

Secretions from these animals have been traditionally used to target diseases of the immune, hematological, and nervous systems. Many of the pharmacologically active constituents identified in these preparations are peptides and proteins, including antimicrobial peptides (AMPs), thrombolytic and thrombin-like enzymes, immunoregulatory peptides, neurotoxic peptides, antioxidant peptides (AOPs), wound-healing peptides, and protease inhibitors. These molecules often exhibit remarkable potency and target specificity, features that make them exceptionally attractive as scaffolds for drug development and therapeutic innovation (Herzig et al., 2020).

Historically constrained by technological limitations, early practices involving "worm" medicines primarily relied on unrefined applications of whole-animal preparations. The advancement of modern analytical platforms has enabled precise extraction, isolation, and characterization of specific bioactive molecules, thereby clarifying their functional mechanisms and therapeutic potential. A landmark example is captopril, a first-in-class antihypertensive agent developed from snake venom, which acts as an angiotensin-converting enzyme inhibitor (Cushman & Ondetti, 1991, 1999). Another notable case is hirudin, a direct thrombin inhibitor derived from leech saliva, employed clinically as an anticoagulant, especially for individuals who cannot tolerate heparin (Montinari & Minelli, 2022). These translational achievements demonstrate that drug discovery rooted in "worm" medicines derived from venomous and poisonous animals has evolved into a robust and increasingly efficient pipeline for the generation of therapeutic lead compounds.

This review presents a systematic summary of current knowledge on peptide-based agents (≤50 amino acids) isolated from exocrine secretions of venomous and poisonous animals employed as "worm" medicines. Emphasis is placed on their structural diversity, bioactivity profiles, and therapeutic relevance. Inclusion criteria include formal taxonomic identification of the source species, derivation from exocrine secretions, experimental verification of bioactivity, and documentation in authoritative literature. Through this framework, a comprehensive assessment is provided, highlighting these peptides as a largely untapped reservoir for next-generation drug discovery.

TRADITIONAL CHINESE "WORM" MEDICINES DERIVED FROM VENOMOUS AND POISONOUS ANIMALS

Within the unique pharmacopeia of TCM, "worm" medicines encompass a broad assemblage of invertebrate and small vertebrate taxa, many of which produce venom or toxic secretions (Table 1). This group includes centipedes, scorpions, spiders, toads, and certain snakes, which have been employed not only for the management of internal disorders such as pain syndromes, paralysis, and cardiovascular dysfunction but also for the control of parasitic infections, pest-related diseases, and pestilential conditions. These practices reflect long-standing empirical recognition of potent bioactivities associated with venomous organisms. Representative examples of venom-derived "worm" medicines and their therapeutic applications are outlined below.

Hirudinea (leeches)

Dried whole leeches, including *Whitmania pigra* Whitman,

Table 1 Representative pharmacological activities of extracts from representative venomous and poisonous animals used in traditional Chinese "worm" medicines

Common name	Scientific name	Parts used	Indication	References
Invertebrates				
Wasps	*Polistes* spp., *Vespa* spp., *Parapolybia varia*	Venom, Nest	Anticoagulant, antiplatelet, and vasodilatory activities	An et al., 2012
Spiders	*Aranea ventricosus*	Dried whole body	Antiepileptic, anti-inflammatory, analgesic, and antitumor activities	Lian et al., 2018; Liu et al., 2012b
Scorpions	*Buthus martensii*	Dried whole body, Venom	Analgesic, anticoagulant, anticancer, antithrombotic, antiepileptic, and immunoregulatory effects	Wali et al., 2019
Centipedes	*Scolopendra subspinipes mutilans*	Dried whole body	Analgesic, antiepileptic, anti-inflammatory, antithrombotic, and neuroprotective effects	Lee et al., 2025
Leeches	*Whitmania pigra*, *Hirudo* spp., *W. acranulata*	Dried whole body	Anticoagulant, antithrombotic, antiatherosclerotic, antiplatelet aggregation, antitumor and anti-inflammatory activities; improvement of hemorheological parameters	Dong et al., 2016
Amphibians				
Toads	*Bufo gargarizans*	Dried venom, Skin	Cardiotonic, vasoconstriction, analgesic, anti-inflammatory, and anticancer properties	Chan, 1995; Chen & Kovaříková, 1967
Frogs	*Rana spp.*	Whole body, skin, flesh	Wound healing, antimicrobial, antifungal, and anticancer activities	Xu & Lai, 2015
Reptiles				
Snakes	*Deinagkistrodon acutus*, *Bungarus multicinctus*	Dried body, Venom	Anti-inflammatory, analgesic, and meridian-unblocking properties (collateral-dredging)	Liu et al., 2024a

Hirudo nipponica Whitman, and *Whitmania acranulata* Whitman, have been extensively used in TCM to promote blood circulation and resolve blood stasis (Liu et al., 2024a; Wu et al., 2024). Salivary secretions from these annelids contain a highly complex repertoire of bioactive molecules, as revealed by transcriptomic profiling, with a diverse array of anticoagulant and fibrinolytic components. Well-characterized components include hirudin, bdellin, destabilase, and eglin, together with a wide range of less-characterized proteins such as serine protease inhibitors, disintegrin-like peptides, and histidine-rich proteins (Min et al., 2010). Beyond effects on hemostasis, leech-based preparations have been traditionally applied in the treatment of systemic inflammation, rheumatic pain, and certain dermatological diseases (Sig et al., 2017). Historical records trace medicinal use of leeches back to the “Shen Nong Ben Cao Jing”, with continuous clinical application for more than two thousand years in the prevention and management of cardiovascular and cerebrovascular diseases. More than 300 prescriptions incorporating leech material have been documented (Hu et al., 2020), and leeches remain officially listed in the *Chinese Pharmacopoeia* (Dong et al., 2016).

Insecta (wasps, horseflies)

Insects represent a critical and pharmacologically rich component of traditional medicinal systems across global cultures. Within TCM, certain insect species—such as *Polistes* and *Vespa* wasps—have been incorporated into therapies aimed at resolving toxic accumulation, dispersing nodules, and relieving pain. Preparations often involve dried nests or whole-body extracts. Biochemical analyses of wasp venom have identified complex mixtures of biogenic amines, hydrolytic enzymes, and polyamine toxins as key bioactive constituents (Silva et al., 2017). Contemporary pharmacological investigations confirm that peptides derived from wasp venom exert anti-inflammatory, anticoagulant, antiplatelet, and immunosuppressive effects, lending mechanistic support to traditional therapeutic claims (An et al., 2012). Earthworms, commonly referred to as “Dilong” in TCM, have been employed for millennia in dried whole-body form. Representative species, including *Pheretima aspergillum* and *Allolobophora caliginosa*, have been used to clear internal heat, reduce fever, promote diuresis, suppress convulsions, and accelerate tissue regeneration (Cooper et al., 2012; Sun, 2015).

Arachnida (spiders, scorpions)

Spiders, such as *Aranea ventricosus*,have been used in TCM for more than a thousand years, particularly for the treatment of epilepsy, arthritis, and other neurological or inflammatory conditions (Liu et al., 2012b). Their venoms are enriched with peptides characterized by the inhibitor cystine knot motif, a highly stable structural framework that confers exceptional binding specificity and affinity toward a broad array of molecular targets, including voltage-gated calcium (Ca^{2+}), potassium (K^+), and sodium (Na^+) channels, transient receptor potential (TRP) channels, and glutamate receptors (King & Hardy, 2013). Due to their structural complexity, functional selectivity, and potent bioactivities, spider venoms and their derivatives constitute a rich source of pharmaceutical scaffolds, with considerable research interest directed toward their therapeutic application in neurodegenerative, cardiovascular, and pain-related disorders (Escoubas, 2006; King, 2011; Saez et al., 2010).

Scorpions, particularly *Buthus martensii*, are among the most prominent “worm” medicines within TCM, historically used to extinguish wind, relieve convulsions, and remove obstructions in collateral channels. Dried whole-body preparations remain widely employed in decoctions and compound prescriptions. Scorpion venom constitutes a chemically diverse secretome dominated by neurotoxic peptides and proteins targeting ion channels and synaptic transmission. Extracts derived from whole-body materials display a broad spectrum of pharmacological activities, including antinociceptive, anticoagulant, antitumor, antithrombotic, antiepileptic, and immunoregulatory effects (Wali et al., 2019). The therapeutic rationale is grounded in the traditional principle of using controlled toxicity to neutralize pathogenic forces. Recent analytical advances have facilitated direct identification of endogenous peptides from medicinal scorpion preparations, bridging classical applications with contemporary molecular pharmacology (Yang et al., 2019).

Chilopoda (centipedes, millipedes)

The dried body of *Scolopendra subspinipes mutilans* has been used in TCM to resolve toxicity, reduce swelling, and suppress spasms, particularly in conditions such as tetanus and post-stroke sequelae (Chinese Pharmacopoeia Commission, 2020). Proteomic investigations have identified hundreds of venom-derived components with pronounced neuroactivity, many of which selectively interact with the nervous system (Hakim et al., 2015b; Liu et al., 2012a; Rong et al., 2015; Yang et al., 2012). This molecular diversity helps explain the sustained clinical use of centipede-based preparations and their increasing appeal in therapeutic development. Widely used across East Asian medical systems, centipede venoms have been applied to manage ailments ranging from epilepsy and cerebrovascular complications to tetanus and dermatological diseases (Kong et al., 2013a; Pemberton, 1999). As predatory arthropods, centipedes synthesize diverse peptide toxins that selectively target ion channels and synaptic signaling, many of which exhibit pharmacological properties with significant drug development potential (Undheim et al., 2016).

Amphibia (toads, frogs)

Amphibian skin serves as a dynamic interface with fluctuating and often hostile environments, and its secretions play a vital role in defense, physiology, and survival. Over the past several decades, bioactive peptides isolated from these secretions have emerged as a major focus in biomedical research, with over 100 structural families and approximately 2 000 individual peptides identified to date (Bevins & Zasloff, 1990; Xu & Lai, 2015). Within the context of "worm" medicine, dried toad (e.g., *Bufo gargarizans*) secretions from the parotoid and skin glands, known as "Chan Su", have traditionally been used to neutralize toxins, relieve pain, and resolve blockages in the sensory portals (Gao et al., 2016; Qi et al., 2018). Bufadienolides, the major active constituents, demonstrate broad-spectrum bioactivities, including analgesic, anti-inflammatory, and anticancer properties (Chen & Kovaříková, 1967). Skin secretions derived from frog species, such as *Rana nigromaculata* Hallowell and *R. plancyi* Lataste, have historically been applied for heat clearance and detoxification. These secretions contain peptides with diverse therapeutic properties, including wound healing, antimicrobial, antifungal, and anticancer activities (Xu & Lai, 2015).

Reptilia (snakes)

Snakes, comprising approximately 3 789 recognized species across the suborder Serpentes, are distributed globally with the exception of Antarctica (Yacoub et al., 2020). Despite the inherent toxicity of many species, snakes have long been symbolically linked with healing and regeneration, as reflected in enduring medical iconography such as the Rod of Asclepius (Rima et al., 2018). In TCM, snake-derived remedies—typically prepared from the eviscerated and dried body of species including *Agkistrodon acutus*, *Python molurus*, *Ptyas dhumnades*, *Zaocys dhumnades*, *Dinodon rufozonatum*, and *Rhabdophis tigrinus*—are employed for their anti-inflammatory, analgesic, and channel-unblocking properties (Liu et al., 2024a).

EXOCRINE PEPTIDES FROM TRADITIONAL CHINESE "WORM" MEDICINES

Traditional "worm"-based Chinese medicines have demonstrated significant efficacy in clinical practice, increasingly supported by molecular-level research of their active components. Advances in analytical and biochemical approaches have enabled the identification of bioactive peptides that account for many of the observed therapeutic effects. These peptides exhibit remarkable structural and functional diversity, with activities spanning multiple human physiological systems.

Peptides targeting the cardiovascular system

The cardiovascular system is indispensable for vertebrate survival, mediating oxygen and nutrient delivery, metabolic waste clearance, and immune cell trafficking. Preservation of hemostatic equilibrium within this system is critical for physiological stability. Central to this regulation is the coagulation cascade, a tightly controlled network involving platelet aggregation, vasoconstriction, coagulation, and fibrinolysis (Figure 2), which together ensure rapid containment of vascular injury while minimizing thrombotic risk and hemorrhage.

Over evolutionary timescales, many organisms represented in "worm"-based medicines have developed highly specialized biochemical strategies to modulate hemostatic processes (Table 2). To secure a blood meal, hematophagous species secrete salivary peptides that attenuate coagulation, platelet aggregation, and immune activation, thereby enabling sustained feeding. These secretions contain peptides capable of either promoting or inhibiting discrete steps within hemostatic pathways, highlighting their value as sources of pharmacologically informative compounds (Champagne, 2004; Koh & Kini, 2008). Leeches and other hematophagous species exemplify this strategy through delivery of anticoagulant and immunomodulatory peptides, while venomous snakes deploy peptides that disrupt vascular tone and coagulation dynamics, frequently inducing hypotension and coagulation disorders. This section provides a systematic overview of cardiovascular-active peptides isolated from exocrine secretions of venomous and poisonous "worm" medicines, organized by taxonomic group to facilitate mechanistic comparison and translational interpretation.

Peptides affecting coagulation factors: Thrombosis, a life-threatening condition characterized by intravascular clot formation, remains a major global contributor to cardiovascular morbidity and mortality (Jerjes-Sánchez, 2015). TCM has been used for centuries to manage thrombotic disorders, and recent molecular research has identified a range of antithrombotic peptides from venomous and poisonous species that modulate coagulation pathways with high potency and specificity. These peptides demonstrate remarkable structural diversity and exert their effects through distinct molecular mechanisms.

The leech *Poecilobdella manillensis* produces Poecistasin, a 48-amino acid antistasin-type inhibitor that targets multiple serine proteases—including factor XIIa, kallikrein, trypsin, and elastase—and demonstrates anticoagulant properties and efficacy in alleviating ischemic stroke symptoms in murine models (Tang et al., 2018). From the wasp *Vespa magnifica*, the peptide Magnvesin shows serine protease-like activity and hydrolyzes key clotting factors, reducing coagulation potential (Han et al., 2008). In parallel, transcriptomic and proteomic analyses of horsefly salivary glands identified Tabserin, a serine protease capable of dose-dependent inhibition of coagulation cascades (Xu et al., 2008). The centipede

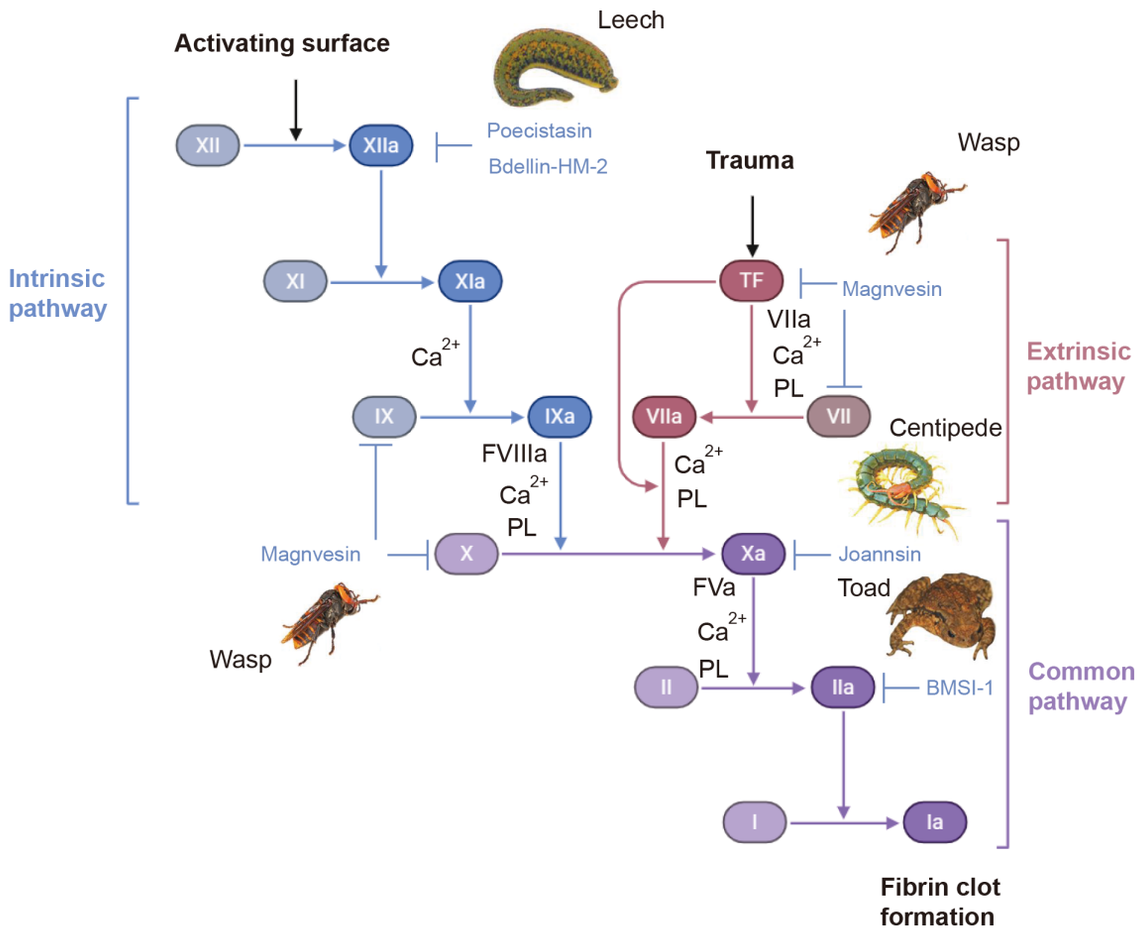

Figure 2 Schematic of the coagulation cascade and its modulation by peptides derived from venomous animals used in traditional Chinese "worm" medicines

Intrinsic pathway (left) is triggered by contact activation and involves factors XII, XI, IX, and VIII, along with Ca^{2+} and phospholipids (PL). Extrinsic pathway (right) is triggered by trauma and involves tissue factor (TF) and factor VII. Both pathways converge into the common cascade, leading to the generation of factor Xa, thrombin (IIa), and fibrin clot formation. Peptides from leech, wasp, centipede, and toad venoms target specific coagulation factors at various stages of the cascade (Created in BioRender. Luo, L. (2025) https://BioRender.com/1tevy79).

Table 2 Representative peptides with cardiovascular activity

UniProt ID	Name	Sequence	Activity	Species	References
–	TNGYT	TNGYT	Anticoagulant activity	*Scolopendra subspinipes mutilans* (Chinese red-headed centipede)	Kong et al., 2013b
B3TFE9	Odorranalectin	YASPKCFRYPNGVLACT	Platelet aggregation–inhibition	*Odorrana grahami* (Graham's frog)	Li et al., 2008a
–	ZDPI	FRGCWLKNYSPRGCL	Antiplatelet activity	*Amolops loloensis* (rufous-spotted torrent frog)	Hao et al., 2016
–	Poecistasin	ADCGGKTCSGGQVCSDGV CVCTKLRCRLLCRNGFLKD ENGCEYPCTCA	Anticoagulant activity	*Poecilobdella manillensis* (Asian buffalo leech)	Tang et al., 2018

–: Not available.

Prospirobolus bungii produces Joannsin, a Kunitz-type protease inhibitor stabilized by three disulfide bridges, which potently inhibits trypsin and FXa and exhibits significant antithrombotic activity *in vitro* and *in vivo* (Luan et al., 2017). Another FXa-targeting peptide, TNGYT, purified from *S. subspinipes mutilans*, significantly prolongs activated partial thromboplastin time and prothrombin time, and delays clot formation and bleeding cessation in murine models (Kong et al., 2013a; Kong et al., 2013b). Amphibian skin also provides a rich reservoir of bioactive protease inhibitors. BMSI-1 and BMSI-2, isolated from *Bombina microdeladigitora*, each contain five disulfide bonds derived from 10 half-cystines. BMSI-1 exhibits strong inhibition of both trypsin and thrombin, with K_i values of 0.02 μmol/L and 0.15 μmol/L, respectively (Lu et al., 2008).

Peptides affecting platelets: *Antiplatelet aggregation peptides*: In addition to direct effects on coagulation factors, numerous bioactive peptides isolated from venomous and poisonous species used in traditional "worm" medicines regulate hemostasis through platelet function modulation. These antiplatelet agents are taxonomically widespread, with key examples identified in insects, amphibians, and reptiles. Functional inhibition of platelet aggregation represents a critical antithrombotic mechanism, and the peptides involved often exhibit unique structural features and molecular targets. Multi-omics analyses of salivary glands from the horsefly

Tabanus yao have uncovered several novel peptide families with antiplatelet activity. Among these, Tabinhibitins 1 and 2 form a distinct class of aggregation inhibitors that appear to disrupt platelet function through a previously uncharacterized mechanism involving direct interaction with the platelet membrane. In amphibians, a 15-amino-acid peptide, Zongdian platelet inhibitor (ZDPI), isolated from the skin secretions of *Amolops loloensis* features an intramolecular disulfide bond and C-terminal amidation (Hao et al., 2016), structural features that likely contribute to its bioactivity. This discovery extends the known functional repertoire of amphibian-derived peptides and underscores evolutionary convergence of antiplatelet mechanisms across venomous and toxic lineages.

Disintegrin: Disintegrins, a structurally conserved protein family found predominantly in snake venom, represent a potent class of antiplatelet agents within the pharmacological landscape of TCM. These peptides interfere with integrin-mediated cell adhesion and platelet aggregation (Lu et al., 2005; McLane et al., 2004) by binding to integrin receptors essential for intercellular and matrix interactions that support platelet bridging and contribute to thrombosis and hemostasis. Disintegrins are defined by conserved recognition motifs, typically RGD or KGD sequences, which confer high-affinity binding to the integrin $\alpha_{IIb}\beta_3$ on the platelet surface, effectively preventing fibrinogen attachment and suppressing platelet aggregation (Reiss et al., 2006; Scarborough et al., 1993). One of the most potent examples, Eristostatin from *Echis carinatus*, acts as a high-affinity antagonist of $\alpha_{IIb}\beta_3$, preventing ADP-induced platelet activation and aggregation through selective integrin binding (Pfaff et al., 1994).

Platelet aggregation activators: In contrast to antiplatelet agents, several venom- and secretion-derived proteins function as potent platelet aggregation promoters, contributing to thrombus formation through distinct molecular pathways. One such example is Magnifin, a phospholipase-like protein identified from the venom of *V. magnifica*, which enhances platelet aggregation and promotes thrombosis *in vivo*. Magnifin shares high sequence similarity to A_1 (PLA_1) allergens found in other wasp species (Yang et al., 2008), implicating conserved prothrombotic functions across Hymenoptera. Sugar-binding lectins have also been extensively studied for their roles in drug targeting and delivery (Xu & Lai, 2015). Odorranalectin, isolated from skin secretions of *Odorrana grahami*, exhibits specific high-affinity binding to L-fucose residues, enabling targeted delivery to the liver, spleen, and lungs following intravenous injection (Li et al., 2008a). Among venom-derived lectin-like proteins, snake C-type lectin-like proteins (snaclecs) constitute a major functional group with direct regulatory roles in thrombosis and hemostasis. Mucetin and stejnulxin, purified from the venom of *Protobothrops mucrosquamatus* and *Trimeresurus stejnegeri*, respectively, induce robust platelet degranulation and accelerate clot retraction *in vitro*. In animal models, systemic administration of these peptides leads to widespread microvascular thrombosis, reduced cerebral perfusion, and motor and cognitive deficits, closely resembling thrombotic microangiopathy observed in envenomated patients. Notably, antibody-based neutralization of these proteins significantly attenuates platelet activation and ameliorates associated pathologies (Lee et al., 2003; Long et al., 2020; Tian et al., 2020).

Peptides targeting the immune system

The immune system is essential for vertebrate survival. Notably, many organisms used in “worm”-based medicines have evolved highly specialized biochemical strategies to modulate immune processes. The array of peptides that target the immune system in these medicines include antimicrobial, myotropic, immunoregulatory, antiviral, and antimalarial peptides (Table 3).

Antimicrobial peptides: The rapid global expansion of antimicrobial resistance presents a critical challenge to modern medicine, highlighting the urgent need for innovative therapeutic approaches. AMPs represent evolutionarily conserved effectors of innate immunity and offer a compelling alternative to conventional antibiotics through multimodal mechanisms that disrupt microbial viability while simultaneously modulating host immune responses. This section reviews AMPs derived from the exocrine secretions of venomous and poisonous organisms employed in traditional Chinese “worm” medicines, organized according to taxonomic classification.

Venoms from diverse animal lineages, including arthropods, amphibians, and reptiles, constitute rich reservoirs of AMPs. These molecules are typically short, cationic peptides that exert broad-spectrum activity by disrupting microbial membrane integrity, thereby targeting bacteria, fungi, and, in some cases, parasitic organisms (Erdem Büyükkiraz & Kesmen, 2022; Mwangi et al., 2023, 2025). Venom from *V. magnifica* contains peptide families with potent antimicrobial and antifungal activities accompanied by minimal hemolytic effects (Xu et al., 2006b). In the scorpion *B. martensii*, four disulfide-free peptides have been identified, among which the basic, C-terminally amidated BmKn2 exhibits strong antimicrobial potency, whereas BmKb1 displays comparatively weaker activity (Zeng et al., 2004).

Amphibian skin secretions represent the most extensive known source of AMPs, providing immediate chemical defense against microbial invasion through peptides typically ranging from 10–50 amino acids in length (Conlon et al., 2004; Duda et al., 2002). Skin secretions from *O. grahami* yield peptides featuring distinctive disulfide-linked hexapeptide motifs with broad antimicrobial activity, with the exception of activity against *Escherichia coli* (Che et al., 2008). The same species produces Odorranain-HP, which displays antimicrobial efficacy against several pathogens, including *Helicobacter pylori* (Chen et al., 2007). Species within the genus *Amolops*, adapted to fast-flowing environments through expanded adhesive toe discs, produce a diverse array of AMPs. *A. loloensis* secretes Cathelicidin-AL, a 48-residue cationic peptide active against a wide spectrum of bacteria and fungi, including multidrug-resistant clinical isolates (Hao et al., 2012). Additional AMP families from this species include Amolopins, Esculentin-2-AL (two isoforms), and Temporin-AL (three isoforms), all showing antimicrobial properties (Wang et al., 2010). Further isolates comprise Brevinins-ALa–d and Temporins-ALa–c, with Brevinin-ALb exhibiting pronounced hemolytic activity that is absent in Temporin-Ma (Lu et al., 2006). Skin secretions from *A. jingdongensis* have yielded 31 AMPs categorized into nine distinct groups, including the novel Jingdongin-1 and -2 families, both demonstrating potent efficacy against diverse bacteria and fungi (He et al., 2013).

Studies on *R. nigrovittata* have identified Brevinin-2-RN1 and Brevinin-2-RN2, which exhibit potent activity against Gram-positive and Gram-negative bacteria as well as fungi (Liu et al., 2011). *Rana grahami* additionally produces Grahamin-1 and Grahamin-2, both characterized by broad antimicrobial potency (Xu et al., 2006a). From *Hylarana*

Table 3 Representative peptides acting on the immune system

UniProt ID	Name	Sequence	Activity	Species	References
–	Odorranain-NR	GLLSGILGAGKHIVCGLTGCAKA	Antimicrobial	*Odorrana grahami* (Graham's frog)	Che et al., 2008
–	Odorranain-HP	GLLRASSVWGRKYYVDLAGCAKA	Antimicrobial	*O. grahami* (Graham's frog)	Chen et al., 2007
R4QZ32	Pleurain-a1-thel	RILTMTKRVKMPQLYKQIVCRLFKTC	Antimicrobial	*Theloderma corticale* (Kwangsi warty tree frog)	Yan et al., 2013
I1T028	Cathelicidin-AL	RRSRRGRGGGRRGGSGGRGGRGGGGRSGAGSSIAGVGSRGGGGGRHYA	Antimicrobial	*Amolops loloensis* (Lolokou sucker frog)	Hao et al., 2012
–	Amolopins	NILSSIVNGINRALSFFG	Antimicrobial	*A. loloensis* (Lolokou sucker frog)	Wang et al., 2008a
C5H0D4	Esculentin-2-ALa	GIFALIKTAAKFVGKNLLKQAGKAGLEHLACKANNQC	Antimicrobial	*A. loloensis* (Lolokou sucker frog)	Wang et al., 2010
C5H0D6	Temporin-ALd	FLPIAGKLLSGLSGLL	Antimicrobial	*A. loloensis* (Lolokou sucker frog)	Wang et al., 2010
–	Brevinin-ALb	FLPLAVSLAANFLPKLFCKITKKC	Antimicrobial	*A. loloensis* (Lolokou sucker frog)	Lu et al., 2006
–	Temporin-ALa	FLPIVGKLLSGLSGLL-NH_2	Antimicrobial	*A. loloensis* (Lolokou sucker frog)	Lu et al., 2006
E1AZ82	Amolopkinin	RAPVPPGFTPFR	Ileal contraction	*A. loloensis* (Lolokou sucker frog)	Liang et al., 2006
K7ZGS2	Jingdongin-1	FLPIVENCSLVCWENNQKC	Antimicrobial	*A. jingdongensis* (Chinese torrent frog)	He et al., 2013
M9MMP3	Cathelicidin-PY	RKCNFLCKLKEKLRTVITSHIDKVLRPQG	Antimicrobial	*Rana catesbeiana* (American bullfrog)	Wei et al., 2013
C3RT22	Temporin-LK1	FFPLLFGALSSMMPKLF	Antibacterial and antifungal	*Limnonectes kuhlii* (Kuhl's creek frog)	Wang et al., 2013
–	Brevinin-2-RN1	GAFGNFLKGVAKKAGLKILSIAQCKLSGTC	Antibacterial and antifungal	*R. nigrovittata* (black-striped frog)	Liu et al., 2011
P86093	Ranakinin-N	RAEAVPPGFTPFR	Ileal contraction	*R. nigrovittata* (black-striped frog)	Liu et al., 2008
P85071	Grahamin 1	GLLSGILGAGKHIVCGLSGLC	Antibacterial and antifungal	*R. grahami* (Graham's frog)	Xu et al., 2006a
K7WVG6	Polypedarelaxin 1	QGGLLGKVSNLANDALGILPI	Ileal contraction	*Polypedates pingbianensis (tree frog)*	Meng et al., 2012
I6R7Y9	Polypedatein	TLLCKYFAIC	Ileal contraction	*P. pingbianensis* (tree frog)	Yan et al., 2012
A0A6M4CA40	Brevinin-1GHd	FLGALFKVASKLVPAAICSISKKC	Antibacterial and anticancer	*Hylarana guentheri* (*Sylvirana guentheri*)	Jiang et al., 2020
A0A3G6VAR4	Esculentin-1GN	GLFSKKGGKGGKSWIKGVFKGIKGIGKEVGGDVIRTGIEIAACKIKGEC	Antibacterial and anti-inflammation	*H. guentheri* (*Sylvirana guentheri*)	Zeng et al., 2018
Q8JHE1	Maximin H5	ILGPVLGLVSDTLDDVLGIL-NH_2	Antibacterial	*Bombina maxima* (giant fire-bellied toad)	Lai et al., 2002c
B6D434	Cathelicidin-BF	KFFRKLKKSVKKRAKEFFKKPRVIGVSIPF	Antibacterial	*B. fasciatus* (banded krait)	Wang et al., 2008b, 2011
P0C1M1	5e	FLPIIAKLLGGLL	Antibacterial and antifungal	*Vespa magnifica* (hornet)	Xu et al., 2006b
P0C1M4	12a	INWKGIAAMAKKLL	Antibacterial and antifungal	*V. magnifica* (hornet)	Xu et al., 2006b
–	Neuropeptide Y-HS	FLEPPERPAVFTSVEQMKSYIKALNDYYLLLGRPRF-NH_2	Anti-inflammation	*Haemadipsa sylvestris* (Indian leech)	Liu et al., 2016
–	Immunoregulin HA	EAQFEDLVTGYLRKGGVTGVTEFEPVDVSGEDYDSDEMDEDGRA	Anti-inflammation	*Hybomitra atriperoides* (horsefly)	Yan et al., 2008
A0A5Q1NCA8	Av-LCTX-An1a	GFGCPLDQMQCHNHCQSVRYRGGYCTNFLKMTCKCY	Antiviral	*Alopecosa nagpag* (wolf spider)	Ji et al., 2019
C1IBZ3	Tabimmunregulins 1	GGVSGVSDFEPIEVFGEDYDSDEADEDGKG	Anti-inflammation	*Tabanus yao* (horsefly)	Xu et al., 2008
Q6JQN2	BmKn2	LLFLVVLLLAISQSDA	Antibacterial	*Olivierus martensii* (Manchurian scorpion)	Zeng et al., 2004

–: Not available.

guentheri, Brevinin-1GHd shows strong antimicrobial activity with minimal hemolysis (Jiang et al., 2020), whereas Esculentin-1GN adopts a highly amphipathic helical structure and exhibits robust microbicidal capacity (Zeng et al., 2018). Investigations of *Paa yunnanensis* identified Cathelicidin-PY, which combines strong antimicrobial potency with minimal hemolysis and notable anti-inflammatory effects (Wei et al., 2013). *Limnonectes kuhlii* produces multiple AMPs including Temporin-LK1, Rugosin-LK1, Rugosin-LK2, Gaegurin-LK1, and Gaegurin-LK2, most of which exhibit broad-spectrum properties (Wang et al., 2013). In *Bombina maxima*, PR-bombesin exhibits an unusual N-terminal structure suggestive of microbial targeting capability (Li et al., 2006b), while Maximin H5 shows selective antimicrobial activity against *Staphylococcus aureus* without detectable effects on other tested bacterial or fungal strains (Lai et al., 2002c).

Reptile-derived AMPs also represent a diverse and biologically significant group of molecules with innate immune defenses. Venom from *Bungarus fasciatus* contains Cathelicidin-BF, which demonstrates broad-spectrum antimicrobial efficacy against diverse bacteria and fungi (Wang et al., 2008b), including drug-resistant clinical isolates

and saprophytic species, and shows therapeutic potential in the treatment of acne vulgaris (Wang et al., 2011). Collectively, these findings underscore the exceptional diversity of AMPs within traditional Chinese "worm" medicines and highlight their substantial promise as templates for next-generation anti-infective therapeutics.

Myotropic peptides: Myotropic peptides, including Bombesin, Bradykinin (BK), Tachykinin (TK), Tryptophyllin, Caerulein, and Cholecystokinin (CCK), play essential roles in animal physiology and defense mechanisms by modulating smooth muscle contractility. These molecules induce characteristic contractile responses in isolated smooth muscle tissues, most notably the ileum, making them valuable pharmacological probes in functional assays.

Bombesin-like peptides (BLPs): BLPs constitute a class of neuroendocrine peptides that regulate smooth muscle activity and exhibit diverse biological effects. Amphibian skin secretions have yielded numerous BLP variants. In *O. grahami*, five mature peptides (B1–B5) have been characterized, with B1–B3 shown to elicit contractions in isolated rat stomach strips, while B4 and B5 exert inhibitory effects, reflecting functional heterogeneity within this family (Li et al., 2007). *Hylarana latouchii* secretes Ranatensin-HL, with both its full-length form and a C-terminal decapeptide capable of inducing mild contractions in rat bladder and uterine smooth muscle preparations (Lin et al., 2017). In *Bombina maxima*, PR-bombesin features a distinctive proline-rich N-terminal octapeptide containing four prolines and three basic residues (Lai et al., 2002a).

Bradykinin (BK)-related peptides: BK, a nine-residue peptide of the kinin family, induces arteriolar dilation through prostacyclin, nitric oxide, and endothelium-derived hyperpolarizing factor, while promoting venous constriction via prostaglandin F_2 release, collectively increasing capillary permeability and inflammatory responses. Several BK analogs have been isolated from amphibians. In *Bombina maxima*, Bombinakinin-GAP, a 28-residue peptide containing an intramolecular disulfide bond, suppresses food intake when administered intracerebroventricularly (Lai et al., 2003a). *A. loloensis* produces Amolopkinin, a 12-residue peptide that induces dose-dependent contractions in isolated guinea pig ileum (Liang et al., 2006). Similarly, Ranakinin-N from *R. nigrovittata* evokes comparable contractile responses in the same model (Liu et al., 2008).

Cholecystokinins (CCKs): CCKs are neuroendocrine peptides primarily distributed in the gastrointestinal tract and central nervous system of vertebrates. Amphibian homologs have been identified in *R. catesbeiana*, *Xenopus laevis*, and *R. nigrovittata*, showing high sequence identity with mammalian CCKs, including conserved sulfated tyrosine residues essential for biological activity (Johnsen, 1994; Liu et al., 2007). The CCK analog isolated from *R. nigrovittata* is identical to mammalian brain and gut CCK, supporting the existence of a skin-gut-brain peptide network in amphibians (Liu et al., 2007). Functionally, amphibian CCKs regulate digestive physiology by stimulating pancreatic enzyme release and modulating gallbladder motility, showing functional divergence from structurally related gastrins (May et al., 1978; Nielsen et al., 1998).

Other myotropic peptides: Several additional peptides have exhibited myotropic activity in isolated smooth muscle models. Notably, peptides have been identified from the skin secretions of *Polypedates pingbianensis*, including Polypedarelaxin 1 and Polypedatein, and from *Bombina maxima*, including two Bv8-like peptides (Bv8-LP1 and Bv8-LP2). Polypedarelaxin 1, a 21-residue peptide, induces concentration-dependent relaxation in rat ileum, with no detectable antimicrobial or serine protease inhibitory activity (Meng et al., 2012), while Polypedatein has also been characterized as myotropic (Yan et al., 2012). Bv8-LP1 and Bv8-LP2, isolated from the epidermal secretions of the toad *Bombina maxima*, functionally induce ileal contractions in guinea pigs similar to native Bv8, and cause dose-dependent contraction of rabbit aortic rings at nanomolar concentrations (Lai et al., 2003b).

Immunoregulatory peptides: Hematophagous species have evolved highly specialized molecular mechanisms to subvert host immune defenses and facilitate blood acquisition. Among these, salivary peptides exert immunoregulatory effects through selective inhibition of proinflammatory signaling cascades. Neuropeptide Y-HS, a 36-residue amidated peptide isolated from *Haemadipsa sylvestris*, demonstrates potent anti-inflammatory activity by suppressing the secretion of multiple pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) (Liu et al., 2016). In a comparable mechanism, Immunoregulin HA, identified from *Hybomitra atriperoides*, modulates lipopolysaccharide (LPS)-induced immune activation in rat splenocytes by down-regulating IFN-γ and MCP-1 levels while concurrently up-regulating the expression of the anti-inflammatory cytokine IL-10 (Yan et al., 2008).

Antiviral peptides: Exocrine secretions from venomous species serve as a reservoir of antiviral peptides that interfere with diverse stages of viral infection, including entry, replication, and release (Da Mata et al., 2017; Lima et al., 2022). Scorpion-derived peptides such as BmKn2-T5 suppress early infection by enterovirus 71 and other enveloped viruses, exhibiting broad-spectrum activity with minimal cytotoxicity (Xia et al., 2024). Several scorpion peptides also display high-affinity binding to the SARS-CoV-2 spike glycoprotein, highlighting their promise for coronavirus-targeted therapeutic development (Ghazal et al., 2024; Soorki, 2025). In arachnids, the spider *Alopecosa nagpag* produces Av-LCTX-An1a, a defense peptide that effectively suppresses Zika virus (ZIKV) infection through specific inhibition of viral NS2B-NS3 protease activity (Ji et al., 2019). Reptiles are also rich sources of antiviral peptides. Cathelicidin-BF from *Bungarus fasciatus* venom inspired the design of ZY13, a synthetic analog that demonstrates potent anti-ZIKV activity in both cellular and animal models. ZY13 neutralizes viral particles, reduces virion production, and enhances host antiviral responses through modulation of the AXL receptor tyrosine kinase-suppressor of the cytokine signaling cascade (Xing et al., 2020).

Antimalarial peptides: Malaria remains a severe global health threat caused by *Plasmodium* parasites, primarily the highly pathogenic species *P. falciparum*. Natural peptides derived from traditional "worm" medicines represent promising therapeutic candidates with reduced risk of resistance compared to conventional antimalarial drugs. Two linear cationic peptides, meucin-24 and meucin-25, isolated from the venom gland of the scorpion *Mesobuthus eupeus*, inhibit intraerythrocytic *P. falciparum* development with high specificity and minimal cytotoxicity to mammalian cells, indicating strong therapeutic potential (Díaz-Gómez et al.,

2024). Similarly, Psalmopeotoxins I and II, isolated from the tarantula *Psalmopoeus cambridgei*, inhibit *P. falciparum* proliferation at low micromolar concentrations by specifically targeting infected erythrocytes, while exhibiting negligible hemolytic or systemic toxicity (Choi et al., 2004). Snake venom-derived peptides, including LZ1 from cathelicidin precursors, demonstrate potent *in vitro* and *in vivo* antimalarial effects by selectively inhibiting parasite metabolism and reducing inflammation during infection (Fang et al., 2019). Integrative strategies involving *in silico* modeling and rational peptide engineering are accelerating the development of optimized venom-based therapeutics with enhanced selectivity, bioavailability, and safety profiles (Samy et al., 2017).

Peptides targeting the nervous system

Venomous species have evolved a variety of neuroactive peptides to immobilize prey and deter predators. A central mechanism involves the modulation of ion channels, which govern neuronal excitability and synaptic transmission (Figure 3). This section provides an overview of channel-modulating peptides derived from traditional Chinese "worm" medicines (Table 4).

TRP channel modulators: Several "worm" medicine-derived peptides specifically modulate transient receptor potential vanilloid 1 (TRPV1) by binding to its outer pore region, altering its gating properties and amplifying nociceptive signaling, thereby offering templates for novel analgesic development. The Chinese red-headed centipede *S. subspinipes mutilans* yields RhTx, a 27-residue peptide with a compact polarized structure that activates TRPV1 with high affinity and rapid binding kinetics. This peptide specifically targets the heat-sensing domain of the channel, inducing pronounced thermal hypersensitivity at physiological temperatures through robust binding of its strongly cationic C-terminal segment to the electropositive outer pore domain (Yang et al., 2015). In *B. martensii*, the 29-amino-acid peptide BmP01 adopts a compact α-helix and β-strand structure stabilized by three disulfide bonds (Hakim et al., 2015a). BmP01 displays dual functionality: it displayed less inhibition of K_V channels and increasing activation of TRPV1 with pH decrease. Binding to a known proton-sensing site on TRPV1, BmP01 potently activate this nociceptive channel in synergy with extracellular protons, a feature likely contributing to the intense pain elicited by scorpion envenomation (Yang et al., 2017).

Voltage-gated sodium (Na_V) channel modulators: Peptides from venomous species traditionally employed in Chinese "worm" medicines exhibit potent and subtype-selective modulation of Na_V channels, which are central to neuronal excitability and pain transmission. In the leech *Haemadipsa sylvestris*, the HSTX peptide family (22–25 amino acids, C-terminal amidation, two disulfide bonds) includes HSTX-I, which selectively inhibits $Na_V1.8$ and $Na_V1.9$ channels, producing robust analgesia in animal models (Wang et al., 2018). The spider *Haplopelma lividum* produces μ-TRTX-Hl1a, a peptide that selectively suppresses tetrodotoxin (TTX)-resistant Na_V currents, most notably $Na_V1.8$ (IC_{50}= 2.19 μmol/L), while sparing TTX-sensitive isoforms (Meng et al., 2016). The scorpion *B. martensii* yields α-toxin BmK-M9, which induces irreversible activation of skeletal muscle Na_V channels through a membrane delivery pathway (Li et al., 2019). In *S. subspinipes mutilans*, μ-SLPTX-Ssm6a exhibits

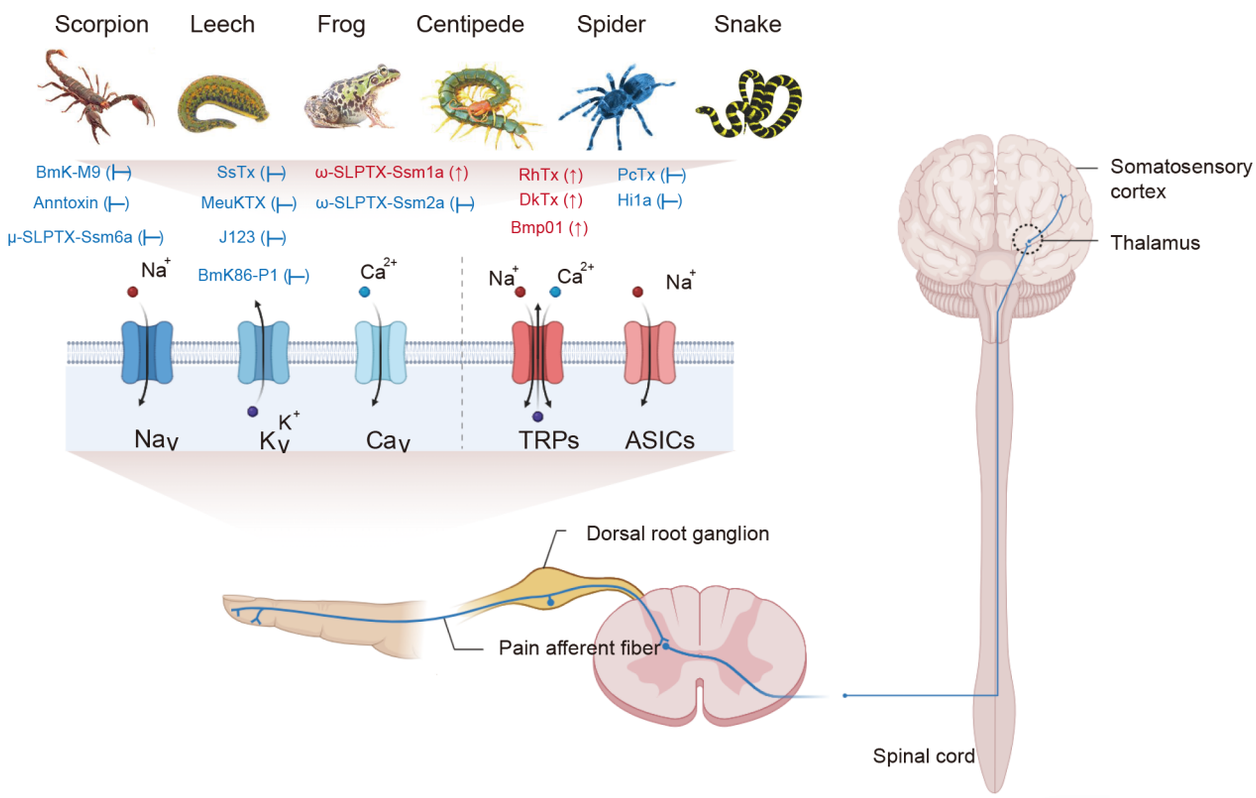

Figure 3 Schematic showing venom-derived modulation of ion channels on nociceptive neurons

Venoms from scorpions, spiders, snakes, centipedes, frogs, and leeches target ion channels including Na_V, Ca_V, K_V, TRP channels, and ASICs on dorsal root ganglion (DRG) neurons. This alters Na^+, Ca^{2+}, or K^+ flux and triggers neuronal excitation (Created with BioRender at https://BioRender.com/4tcick2).

Table 4 Representative peptides acting on the nervous system

UniProt ID	Name	Sequence	Activity	Species	References
–	RhTx	LNNPCNGVTCPSGYRCSIVDKQCIKKE	Activator of TRPV1 channels	*Scolopendra mutilans* (Chinese red-headed centipede)	Yang et al., 2015
–	μ-SLPTX-Ssm6a	ADNKCENSLRREIACGQCRDKVKTDG YFYECCTSDSTFKKCQDLLH	Potent inhibitor of $Na_V1.7$ channels	*S. mutilans* (Chinese red-headed centipede)	Yang et al., 2013
–	μ-SLPTX-Ssm1a	ADNKFENSLRREIACGQCRDKVKCDP YFYHCG	Inhibitor of (TTX-S) Na^+ channels	*S. mutilans* (Chinese red-headed centipede)	Yang et al., 2012
P56852	Hanatoxin	ECRYLFGGCKTTSDCCKHLGCKFRDK YCAWDFTFS	Inhibitor of $K_V2.1$, $K_V4.2$ and $Ca_V2.1$ channels	*Grammostola rosea* (Chilean rose tarantula)	Swartz & MacKinnon, 1997a
I6RA66	κ-SLPTX-Ssm2a	AQNHYCKEHNCPPGKHCPKVPIVCVY GPCCF	Inhibitor of K^+ channels	*S. mutilans* (Chinese red-headed centipede)	Yang et al., 2012
Q9U8D2	BmP01	ATCEDCPEHCATQNARAKCDNDKCVC EPK	Activator of TRPV1 channels, inhibitor of $K_V1.3$ channels	*Olivierus martensii* (Manchurian scorpion)	Hakim et al., 2015a; Yang et al., 2015
–	μ-TRTX-Hl1a	TECGKKTWPCETSEDCCDGDCSDTY WTCHLGFGCTRICV	Inhibitor of (TTX-R) Na^+ channels	*Haplopelma lividum* (cobalt blue tarantula)	Meng et al., 2016
–	HSTXs	ACKEYWECGAFLFCIEGICVPMI	Inhibitors of $Na_V1.8$ and $Na_V1.9$ channels	*Haemadipsa sylvestris* (Indian leech)	Wang et al., 2018
P60514	PcTx1	EDCIPKWKGCVNRHGDCCEGLECWK RRRSFEVCVPKTPKT	Inhibitor of ASIC1a channels	*Psalmopoeus cambridgei* (Trinidad chevron tarantula)	Escoubas et al., 2000; Saez et al., 2011

–: Not available.

exceptional specificity for human $Na_V1.7$ (IC_{50}=25 nmol/L) with over 150-fold discrimination against other Na_V subtypes. In murine pain models, μ-SLPTX-Ssm6a outperforms morphine in chemically induced nociception and shows comparable efficacy in thermal and acid-induced pain paradigms (Yang et al., 2013). Another neurotoxic peptide from the same species, μ-SLPTX-Ssm1a (MW 3762.5 Da), preferentially blocks TTX-sensitive Na_V channels (IC_{50}=9 nmol/L) (Yang et al., 2012). *Hyla annectans* skin secretions produce Anntoxin, which constitutes the first genetically encoded neurotoxic peptide discovered in amphibians and functions as a specific antagonist of TTX-sensitive Na_V channels (Wei et al., 2011).

Voltage-gated potassium (K_V) channel modulators: Peptides derived from venomous animals used in traditional Chinese "worm" medicines modulate K_V channels, which are essential regulators of neuronal excitability and immune cell activation. These modulators operate via diverse mechanisms, including direct occlusion of the pore and allosteric alteration of voltage sensor functions. Canonical inhibitors include charybdotoxin from scorpions and hanatoxin from tarantulas, which illustrate distinct inhibitory strategies. Hanatoxin alters voltage-dependent gating by engaging voltage-sensing residues within the S3–S4 transmembrane helices (Alabi et al., 2007; Swartz & MacKinnon, 1997a, 1997b), while charybdotoxin blocks the external pore (Garcia et al., 1994; Miller, 1995; Swartz, 2007). From *B. martensii*, BmK86-P1 selectively inhibits $K_V1.2$ with high potency (IC_{50}=28.5 nmol/L) and exhibits remarkable thermostability, which may enhance medicinal processing resilience (Qin et al., 2021). Another peptide from this species, J123, targets $K_V1.3$ channels with subnanomolar efficacy (IC_{50}=0.79 nmol/L) (Yin et al., 2008). The scorpion *Mesobuthus martensii* produces Mesomartoxin, a selective $K_V1.2$ inhibitor with an IC_{50} of 15.6 nmol/L, while venom of *M. eupeus* yields MeuKTX, an effective blocker of $K_V1.1$, $K_V1.2$, and $K_V1.3$ channels (Wang et al., 2015a).

The centipede *S. subspinipes* produces several potent K_V channel-modulating peptides. Notably, κ-SLPTX-Ssm1a and κ-SLPTX-Ssm2a exhibit distinct inhibitory potencies against K_V channels (IC_{50}=44.2±5.7 nmol/L and 570±126 nmol/L, respectively), while κ-SLPTX-Ssm3a partially suppresses K_V currents in dorsal root ganglion (DRG) neurons (25%±5% inhibition at 200 nmol/L) (Yang et al., 2012). Ssm Spooky Toxin (SsTx; MW 6017.5 Da), a 53-residue peptide stabilized by two disulfide bonds (Cys20-Cys46 and Cys24-Cys48), potently blocks potassium voltage-gated channel subfamily Q (KCNQ) channels and contributes to centipede venom lethality (Luo et al., 2018). SsTx also exhibits species-specific channel targeting: it inhibits Shal channels in conspecifics, eliciting reversible, nonlethal effects, but engages Shaker channels in heterospecific prey, inducing fatal paralysis (Yang et al., 2020). Furthermore, SsTx blocks $K_V1.3$ channels, synergistically enhancing the functional disruption caused by K_V7 inhibition (Du et al., 2019).

Voltage-gated calcium (Ca_V) channel modulators: Peptides targeting Ca_V channels represent an emerging therapeutic class for the treatment of neurological disorders and chronic pain, with several already approved for clinical use in conditions such as absence seizures (Zamponi, 2016). The centipede *S. subspinipes* produces two neuropeptides (ω-SLPTX-Ssm1a and ω-SLPTX-Ssm2a) with opposing effects on Ca_V channels. ω-SLPTX-Ssm1a functions as a Ca_V channel activator in DRG neurons, augmenting calcium currents by 70% at lower concentrations and up to 120% at 10 μmol/L. In contrast, ω-SLPTX-Ssm2a functions as a Ca_V channel inhibitor, reducing calcium currents in a dose-dependent manner, suppressing them by 45%±5% at 500 nmol/L and 80% inhibition at 2.5 μmol/L, with an IC_{50} of approximately 1 590 nmol/L in DRG neurons (Yang et al., 2012).

Other channel modulators: In addition to targeting Na_V, K_V, Ca_V, and TRP channels, venomous species used in traditional Chinese "worm" medicines also produce peptides that modulate other ion channel families, including acid-sensing ion channels (ASICs). ASICs are proton-activated cation channels implicated in nociception and neurological disease. Spider venom contains several peptides that target ASIC1a channels via distinct mechanisms. PcTx1, isolated from *P. cambridgei*, exhibits high subtype selectivity and potent blockade of ASIC1a with nanomolar affinity (Escoubas et al., 2000; Saez et al., 2011). Hi1a, a dual-knot peptide from

Hadronyche infensa, suppresses ASIC1a activity in a pH-independent and slowly reversible manner (Chassagnon et al., 2017). Hi1a confers neuroprotection in focal ischemic models by curtailing infarct progression and promoting functional recovery. Collectively, these peptides represent a pharmacologically rich repertoire of ion channel modulators with potential applications in pain management, neurological disease, and cardiovascular therapy.

Peptides targeting other systems

Beyond their roles in modulating the cardiovascular, immune, and nervous systems, bioactive peptides from traditional "worm" medicines demonstrate a remarkably diverse array of pharmacological activities. These include targeting critical processes such as tissue repair, cancer proliferation, and oxidative stress (Table 5).

Wound healing peptides: As the largest organ of the human body, the skin performs diverse physiological functions including osmoregulation, thermoregulation, immune defense, and metabolic waste elimination. Extensive skin damage presents a substantial clinical challenge, necessitating a tightly orchestrated regenerative response involving multiple cell types, growth factors, and cytokines. Amphibian skin exhibits extraordinary regenerative potential and has been extensively used in TCM to promote wound resolution, offering a promising source of pro-healing bioactive peptides.

Tylotoin, isolated from the salamander *Tylototriton verrucosus*, has shown significant wound healing efficacy in full-thickness cutaneous wound models, exhibiting an EC_{50} of 11.14 μg/mL. This peptide promotes keratinocyte, endothelial cell, and fibroblast migration and proliferation, stimulates re-epithelialization and granulation tissue formation, and up-regulates key healing mediators such as transforming growth factor-β1 (TGF-β1) and IL-6 (Mu et al., 2014). From *O. grahami*, CW49 accelerates wound healing in both normal and diabetic models by inducing angiogenesis and mitigating inflammation in hyperglycemic environments (Liu et al., 2014a). AH90, another peptide from the same species, facilitates wound healing by enhancing re-epithelialization and promoting granulation tissue contraction (Liu et al., 2014b).

The frog *A. jingdongensis* produces Bv8-AJ, a member of the Bv8 peptide family that retains the conserved N-terminal 'AVITGA' motif and surpasses epidermal growth factor (EGF) in promoting wound closure by modulating IL-1-mediated signaling (Chang et al., 2019). Amphibian-derived Cathelicidin-OA1 also demonstrates significant antioxidant capacity without inducing direct antimicrobial, hemolytic, or toxic effects, and stimulates proliferation and migration of human keratinocytes and fibroblasts in a dose- and time-dependent manner (Cao et al., 2018).

Anticancer peptides: The sustained global increase in cancer incidence underscores the urgent need for novel therapeutic strategies. Peptides derived from traditional "worm" medicines have attracted growing interest as anticancer agents due to their selective cytotoxicity and mechanistic diversity in targeting tumor cells. Skin secretions from *Bombina orientalis* yield two cationic amphipathic α-helical peptides, BLP-7 and Bombinin H-BO, both processed from a shared Bombinin precursor. These peptides effectively suppress proliferation across multiple human hepatocellular carcinoma cell lines at non-cytotoxic concentrations, demonstrating potential as selective anticancer agents (Zhou et al., 2018). In snake venom, the Cathelicidin-derived peptide LZ1 has been shown to inhibit pancreatic cancer progression by inducing autophagy-mediated cell death, with pharmacological inhibition of autophagy reversing this effect, establishing autophagy induction as the primary mechanism underlying the anticancer activity of LZ1 (Xu et al., 2019).

Antioxidant peptides: AOPs exert their activity primarily through specific amino acid residues, such as tyrosine, tryptophan, cysteine, and histidine, which donate electrons or chelate metal ions to neutralize free radicals. Their efficacy is largely dictated by structural composition rather than secondary conformation.

Twenty-one AOPs from the skin of *L. fragilis*, classified into 11 distinct families, exhibit potent radical scavenging activity against DPPH and $ABTS^+$ and effectively inhibit lipid peroxidation without cytotoxicity. Structural analyses have revealed that these non-hemolytic peptides possess favorable configurations for free-radical neutralization, supporting their utility as templates for antioxidant drug development (Yu et al., 2015). The bullfrog-derived peptide APBSP similarly neutralizes DPPH, hydroxyl, superoxide anion, and peroxyl radicals and sustains lipid peroxidation inhibition in linoleic acid emulsions for over seven days, demonstrating both high stability and low cytotoxicity (Qian et al., 2008; Zhu et al., 2025).

Table 5 Representative peptides acting on other systems

UniProt ID	Name	Sequence	Activity	Species	References
–	Tylotoin	KCVRQNNKRVCK	Wound-healing	*Tylototriton verrucosus*	Mu et al., 2014
A0A2U8ZUL5	Cathelicidin-OA1	IGRDPTWSHLAASCLKCIFDDLPKTHN	Wound-healing and antioxidation	*Odorrana andersonii* (golden crossband frog)	Cao et al., 2018
	AH90	ATAWDFGPHGLLPIRPIRIRPLCG	Wound-healing	*Odorrana grahami*	Liu et al., 2014b
–	CW49	APFRMGICTTN	Angiogenesis and anti-inflammation	*O. grahami*	Liu et al., 2014a
–	Bv8-AJ	AVITGACERDVQCGGGTCCAVSLWMQGLRICTPLGRQG	Wound-healing	*Amolops jingdongensis*	Chang et al., 2019
A0A219CM62	Bombinin H-BO	IIGPVLGLIGKALGGLL	Anticancer and antimicrobial	*Bombina orientalis* (oriental fire-bellied toad)	Zhou et al., 2018
–	APBSP	LEELEEELEGCE	Antioxidation	*Rana catesbeiana* Shaw	Qian et al., 2008
–	Fragilin-A1	VKRRGQDCIHGFCSD	Antioxidation	*Limnonectes fragilis*	Yu et al., 2015
–	Fragilin-B1	GQFNDKRWIPFG	Antioxidation	*L. fragilis*	Yu et al., 2015
–	Odorranain-Q-Lf	APIRMWYMYRKLTDMEPKPVA	Antioxidation	*L. fragilis*	Yu et al., 2015
–	Cath-KP	GCSGRFCNLFNNRRPGRLTLIHRPGGDKRTSTGLIYV	Antioxidation	*Kaloula pulchra*	Lu et al., 2024
C1IBZ0	Metallothionein TY1	MGCKLCENNCKCTSSKCGSVCNCDQSCSCPCKNKSSDQCCK	Antioxidation and antimetal toxicity	*Tabanus yao* (horsefly)	Xu et al., 2008

Several amphibian-derived AOPs exhibit protective efficacy in oxidative stress models. OA-VI12 and Cathelicidin-OA1 demonstrate protective effects against UV- and H_2O_2-induced oxidative damage while promoting wound repair without inducing hemolysis or acute toxicity (Cao et al., 2018; Marrocco et al., 2017). The Cathelicidin-related peptide Cath-KP confers neuroprotection in Parkinson's disease models by activating the Sirt1/Nrf2 pathway, enhancing antioxidant enzyme expression, and reducing mitochondrial and intracellular reactive oxygen species (ROS). Notably, Cath-KP enhances dopaminergic neuron survival, crosses the blood-brain barrier, restores tyrosine hydroxylase-positive neurons, and alleviates motor deficits, supporting its potential for neurodegenerative disease therapy (Lu et al., 2024). Several AOPs have advanced to clinical trials based on their dual capacity to quench ROS and modulate disease-related signaling pathways. Among these, Carnosine, a natural dipeptide with broad-spectrum antioxidant properties, is currently under investigation for diabetic peripheral neuropathy and metabolic disorders (NCT05422352, NCT05329610).

Other bioactive peptides: In addition to the primary functional classes, traditional "worm" medicines encompass a wide array of peptides with distinctive bioactivities and structural features. These molecules provide valuable insights into evolutionary biology and serve as promising candidates for therapeutic exploration or as specialized research tools. Vespakinin, purified from the venom of *V. magnifica*, contains a 168-nucleotide open reading frame, representing the first reported Kininogen gene from an invertebrate (Zhou et al., 2006). The same venom also produces Mastoparans, a class of cationic peptides encoded by precursors such as Mastoparanogen, a 40-residue protein featuring an acidic N-terminal segment and a basic C-terminal Mastoparan domain, with a C-terminal glycine serving as the amidation donor (Xu et al., 2006b).

Comparative sequence analyses have revealed striking homology between vespid chemotactic peptides (VCPs) and Temporin AMPs from the frog *A. loloensis*. Both exhibit antimicrobial and chemotactic functions yet differ in biosynthetic processing: VCPs undergo sequential cleavage by dipeptidyl peptidase IV and trypsin-like proteases, whereas temporins are processed solely by trypsin-like enzymes.

The discovery of TK precursors in *O. grahami* has uncovered a distinct amphibian biosynthetic strategy. Unlike the multi-copy precursors observed in vertebrates and ascidians, these 61-residue molecules encode single mature TKs, such as Tachykinin OG1 and Ranamargarin, featuring conserved FXGLM-NH_2 motifs. This unique architecture provides evolutionary insight into neuropeptide processing mechanisms (Li et al., 2006a). Amphibians also produce diverse protease inhibitors with high specificity. The trypsin inhibitor BMTI from *Bombina maxima* exhibits potent activity (K_i=0.06 μmol/L) (Lai et al., 2002b), while LL-TIL from *Lepidobatrachus laevis* (K_i=16.52 μmol/L) (Wang et al., 2015b), OGTI from *O. grahami* (Li et al., 2008b), and Kunitzin-OV from *O. versabilis* (K_i=3.04 μmol/L) (Dong et al., 2019) represent additional examples. Some of these inhibitors also engage vascular EGF (VEGF)-receptor, offering insights into structure-activity relationships (Zhong et al., 2015).

Collectively, these diverse peptides underscore the exceptional biochemical richness of traditional "worm" medicines. Their varied pharmacological profiles and unique structural characteristics not only enhance our understanding of evolutionary biochemistry but also provide valuable molecular tools for basic research and potential leads for the development of next-generation therapeutics.

TRADITIONAL CHINESE "WORM" MEDICINES AND NOVEL DRUG DEVELOPMENT

Traditional medicines derived from diverse worm-associated species have long provided a rich source of bioactive compounds with high selectivity, potency, and biochemical stability. These molecules have been instrumental in drug discovery and biomedical research, contributing essential diagnostic reagents and research tools. Their ability to modulate specific molecular targets has facilitated elucidation of complex biological systems, such as the coagulation cascade and ion channel dynamics, thereby advancing mechanistic insights into neurological disorders including Parkinson disease, Alzheimer disease, and cerebral ischemia.

Several peptides from venomous species have progressed into clinical development through ongoing pharmacological studies. To date, six venom-derived drugs have received approval from the US Food and Drug Administration. These include Ziconotide (Prialt®), a conotoxin from cone snail venom for chronic pain; Exenatide (Byetta® and Bydureon®), a glucagon-like peptide receptor agonist from *Gila monster* venom for diabetes; and Captopril (Capoten®), an angiotensin-converting enzyme inhibitor originally identified in pit viper venom for hypertension. Other approved agents include Hirudin, an anticoagulant from leech saliva, and the antiplatelet agents Eptifibatide (Integrilin®) and Tirofiban (Aggrastat®), both derived from viper venom components (Jimenez et al., 2018).

In oncology, "worm"-derived traditional medicines represent promising alternatives to conventional chemotherapeutic agents. Given that cancer accounted for approximately 10 million deaths globally in 2020 alone, and current treatments are frequently constrained by toxicity and resistance, these naturally occurring peptides offer structurally and functionally distinct scaffolds for intervention (Serna et al., 2018). Many demonstrate selective cytotoxicity against human cancer cell lines and modulate key oncogenic processes, such as cell proliferation, angiogenesis, and tumor microenvironment remodeling, thereby offering new avenues for anticancer drug development (Moga et al., 2018).

The escalating global prevalence of antimicrobial resistance underscores the urgent need for alternative treatment strategies. Venom-derived AMPs have demonstrated potent clinical activity against multidrug-resistant pathogens, including methicillin-resistant *S. aureus*, carbapenem-resistant *Acinetobacter baumannii*, and vancomycin-resistant enterococci. These peptides exhibit broad-spectrum efficacy against bacterial, fungal, and viral infections, positioning them as promising candidates for clinical development (Jin et al., 2016; Wang et al., 2011). Among them, Cathelicidin-BF, an AMP isolated from the venom of *Bungarus. fasciatus*, a species employed in TCM, has advanced to Phase I clinical trials (Jin et al., 2016; Wang et al., 2008b, 2011). Another Cathelicidin-derived AMP with potent activity against *Pseudomonas aeruginosa* and *Acinetobacter baumannii* is currently under preclinical investigation (Mwangi et al., 2019).

Research into bioactive components secreted by hematophagous animals has significantly expanded our understanding of diverse physiological processes. Several of these molecules have been developed as anticoagulants (e.g.,

Hirudin) or serve as structural templates for the design of therapeutic analogs (e.g., Lepirudin) (Electricwala et al., 1991). These agents are valuable in the study and treatment of cardiovascular disorders and have become integral to drug discovery efforts. In clinical practice, secretions from hematophagous species are frequently employed in microsurgical and reconstructive procedures to alleviate inflammation, relieve venous congestion, and support tissue recovery across a range of documented indications (Sig et al., 2017).

Despite the therapeutic promise of traditional “worm”-derived medicines, several challenges remain regarding their clinical translation. Significant barriers include complex pharmacokinetics, immunogenic potential, and production difficulties that complicate drug development. Sustainable drug discovery strategies must also balance scientific exploration with ecological responsibility, particularly for threatened or endangered species. Such strategies include synthetic peptide production, recombinant expression platforms, and venomics-based discovery pipelines to minimize dependence on wild harvesting.

To address these limitations and accelerate therapeutic advancement, future research should prioritize the integration of modern technologies with traditional knowledge systems. Multi-omics approaches, encompassing proteomics, transcriptomics, genomics, and metabolomics, are essential for comprehensive peptidomics profiling of traditional “worm” medicines. Particular attention should be given to venom proteomics for identifying novel peptides and characterizing post-translational modifications. Combining high-resolution mass spectrometry with next-generation sequencing, as demonstrated in recent venom research (Guan et al., 2025), offers a powerful framework for the systematic annotation of bioactive compounds. Furthermore, machine learning algorithms trained on known venom peptides can facilitate prediction of novel sequences from transcriptomic data, while molecular docking and dynamics simulations can provide insights into structure-function relationships. These computational approaches should be integrated with experimental validation to accelerate the identification of promising candidates.

Future research should also employ systematic approaches to elucidate the molecular mechanisms of identified peptides. Cryo-electron microscopy can help resolve target-bound peptide structures, while chemical biology tools can facilitate target identification. Furthermore, single-cell transcriptomics and proteomics may provide insights into cell-specific responses. To optimize clinical utility, peptide engineering strategies such as cyclization, incorporation of non-canonical amino acids, and nanocarrier-based delivery systems can be implemented to enhance stability, bioavailability, and specificity. Conservation-driven priorities should include scalable alternatives to wild sourcing, such as venom-producing cell lines and engineered synthetic biology platforms, ensuring both biomedical innovation and ecological sustainability.

CONCLUSION

Research into worm-derived TCMs has revealed a broad spectrum of biological activities, reinforcing their value as a source of pharmacologically active compounds. Peptides extracted from these organisms have demonstrated therapeutic potential across cardiovascular, neurological, and immune-related disorders. Nevertheless, their full clinical utility remains underexplored, and their contribution to the holistic efficacy of traditional formulations has not been widely recognized. These peptides exert diverse bioactivities, including antimicrobial and antifungal effects, suppression of tumor growth, modulation of ion channels involved in cardiovascular, neural, immune, and muscular functions, and inhibition of thrombosis. Indeed, TCMs represent a rich and diverse repository of functional bioactive peptides. Collectively, these activities highlight the rich therapeutic potential of “worm”-derived peptides and support their pharmacological relevance in modern drug discovery.

Despite considerable advances in traditional medicine and venom-based therapeutics, the development of “worm”-derived medicines faces persistent challenges. These include incomplete characterization of active components, limited understanding of molecular mechanisms, and restricted access to biological resources amid growing wildlife protection concerns. The inherent complexity of TCM preparations, which typically contain hundreds of chemically diverse compounds derived from whole organisms or crude extracts, further complicates the identification and quantification of trace-level bioactive peptides. Furthermore, natural variability in raw materials contributes to substantial batch-to-batch inconsistency, particularly for peptide-based preparations. Addressing these limitations will require the application of advanced analytical platforms and experimental models. High-throughput and ultra-sensitive technologies are needed to systematically profile bioactive components and establish robust quality control frameworks. Concurrent advances in genomics, transcriptomics, proteomics, and metabolomics will enable unprecedented insights into drug targets and mechanisms of action, foundational elements for rational drug design. Continued integration of modern scientific methodologies with traditional medical knowledge will undoubtedly enhance the contribution of TCM to contemporary healthcare and public health.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS’ CONTRIBUTIONS

All authors contributed to the literature review, manuscript drafting, and revision of the article. All authors read and approved the final version of the manuscript.

REFERENCES

Alabi AA, Bahamonde MI, Jung HJ, et al. 2007. Portability of paddle motif function and pharmacology in voltage sensors. *Nature*, **450**(7168): 370–375.

An S, Chen LL, Wei JF, et al. 2012. Purification and characterization of two new allergens from the venom of *Vespa magnifica*. *PLoS One*, **7**(2): e31920.

Bevins CL, Zasloff M. 1990. Peptides from frog skin. *Annual Review of Biochemistry*, **59**(1): 395–414.

Cao XQ, Wang Y, Wu CY, et al. 2018. Cathelicidin-OA1, a novel antioxidant peptide identified from an amphibian, accelerates skin wound healing. *Scientific Reports*, **8**(1): 943.

Champagne DE. 2004. Antihemostatic strategies of blood-feeding arthropods. *Current Drug Targets-Cardiovascular & Hematological Disorders*, **4**(4): 375–396.

Chan K. 1995. Progress in traditional Chinese medicine. *Trends in Pharmacological Sciences*, **16**(6): 182–187.

Chang JJ, He XQ, Hu JM, et al. 2019. Bv8-like toxin from the frog venom of *Amolops jingdongensis* promotes wound healing via the Interleukin-1 signaling pathway. *Toxins*, **12**(1): 15.

Chassagnon IR, McCarthy CA, Chin YKY, et al. 2017. Potent neuroprotection after stroke afforded by a double-knot spider-venom peptide that inhibits acid-sensing ion channel 1a. *Proceedings of the National Academy of Sciences of the United States of America*, **114**(14): 3750–3755.

Che QL, Zhou Y, Yang HL, et al. 2008. A novel antimicrobial peptide from amphibian skin secretions of *Odorrana grahami*. *Peptides*, **29**(4): 529–535.

Chen KK, Kovaříková A. 1967. Pharmacology and toxicology of toad venom. *Journal of Pharmaceutical Sciences*, **56**(12): 1535–1541.

Chen LH, Li YH, Li JX, et al. 2007. An antimicrobial peptide with antimicrobial activity against *Helicobacter pylori*. *Peptides*, **28**(8): 1527–1531.

Chinese Pharmacopoeia Commission. 2020. Pharmacopoeia of the People' s Republic of China 2020. Beijing: China Medical Science Press, 340–342. (in Chinese)

Choi SJ, Parent R, Guillaume C, et al. 2004. Isolation and characterization of Psalmopeotoxin I and II: two novel antimalarial peptides from the venom of the tarantula *Psalmopoeus cambridgei*. *FEBS Letters*, **572**(1-3): 109–117.

Conlon JM, Kolodziejek J, Nowotny N. 2004. Antimicrobial peptides from ranid frogs: taxonomic and phylogenetic markers and a potential source of new therapeutic agents. *Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics*, **1696**(1): 1–14.

Cooper EL, Balamurugan M, Huang CY, et al. 2012. Earthworms Dilong: ancient, inexpensive, noncontroversial models may help clarify approaches to integrated medicine emphasizing neuroimmune systems. *Evidence-Based Complementary and Alternative Medicine)*, **2012**(1): 164152.

Cushman DW, Ondetti MA. 1991. History of the design of captopril and related inhibitors of angiotensin converting enzyme. *Hypertension*, **17**(4): 589–592.

Cushman DW, Ondetti MA. 1999. Design of angiotensin converting enzyme inhibitors. *Nature Medicine*, **5**(10): 1110–1112.

Da Mata ÉCG, Mourão CBF, Rangel M, et al. 2017. Antiviral activity of animal venom peptides and related compounds. *Journal of Venomous Animals and Toxins including Tropical Diseases*, **23**(1): 3.

Díaz-Gómez JL, Martín-Estal I, Rivera-Aboytes E, et al. 2024. Biomedical applications of synthetic peptides derived from venom of animal origin: a systematic review. *Biomedicine & Pharmacotherapy*, **170**: 116015.

Dong H, Ren JX, Wang JJ, et al. 2016. Chinese medicinal leech: ethnopharmacology, phytochemistry, and pharmacological activities. *Evidence-Based Complementary and Alternative Medicine*, **2016**(1): 7895935.

Dong YJ, Shi DN, Ying Y, et al. 2019. A novel Kunitzin-like trypsin inhibitor isolated from defensive skin secretion of *Odorrana versabilis*. *Biomolecules*, **9**(7): 254.

Du CW, Li JM, Shao ZC, et al. 2019. Centipede KCNQ inhibitor SsTx also targets K_V1.3. *Toxins*, **11**(2): 76.

Duda Jr TF, Vanhoye D, Nicolas P. 2002. Roles of diversifying selection and coordinated evolution in the evolution of amphibian antimicrobial peptides. *Molecular Biology and Evolution*, **19**(6): 858–864.

Electricwala A, Sawyer RT, Jones CP, et al. 1991. Isolation of thrombin inhibitor from the leech *Hirudinaria manillensis*. *Blood Coagulation & Fibrinolysis*, **2**(1): 83–90.

Erdem Büyükkiraz M, Kesmen Z. 2022. Antimicrobial peptides (AMPs): a promising class of antimicrobial compounds. *Journal of Applied Microbiology*, **132**(3): 1573–1596.

Escoubas P. 2006. Molecular diversification in spider venoms: a web of combinatorial peptide libraries. *Molecular Diversity*, **10**(4): 545–554.

Escoubas P, De Weille JR, Lecoq A, et al. 2000. Isolation of a tarantula toxin specific for a class of proton-gated Na^+ channels. *The Journal of Biological Chemistry*, **275**(33): 25116–25121.

Fang YQ, He XQ, Zhang PC, et al. 2019. In vitro and in vivo antimalarial activity of LZ1, a peptide derived from snake cathelicidin. *Toxins*, **11**(7): 379.

Gao F, Xu WF, Tang LP, et al. 2016. Characteristics of *cathelicidin-Bg*, a novel gene expressed in the ear-side gland of *Bufo gargarizans. Genetics and Molecular Research*, **15**(3): gmr. 15038481.

Garcia ML, Garcia-Calvo M, Hidalgo P, et al. 1994. Purification and characterization of three inhibitors of voltage-dependent K^+ channels from *Leiurus quinquestriatus* var. *hebraeus* venom. *Biochemistry*, **33**(22): 6834–6839.

Ghazal A, Clarke D, Abdel-Rahman MA, et al. 2024. Venomous gland transcriptome and venom proteomic analysis of the scorpion *Androctonus amoreuxi* reveal new peptides with anti-SARS-CoV-2 activity. *Peptides*, **173**: 171139.

Goyffon M, Tournier JN. 2014. Scorpions: a presentation. *Toxins*, **6**(7): 2137–2148.

Guan CG, Torres MDT, Li SF, et al. 2025. Computational exploration of global venoms for antimicrobial discovery with Venomics artificial intelligence. *Nature Communications*, **16**(1): 6446.

Hakim MA, Jiang WB, Luo L, et al. 2015a. Scorpion toxin, BmP01, induces pain by targeting TRPV1 channel. *Toxins*, **7**(9): 3671–3687.

Hakim MA, Yang SL, Lai R. 2015b. Centipede venoms and their components: resources for potential therapeutic applications. *Toxins*, **7**(11): 4832–4851.

Han JY, You DW, Xu XQ, et al. 2008. An anticoagulant serine protease from the wasp venom of *Vespa magnifica*. *Toxicon*, **51**(5): 914–922.

Hao X, Tang XP, Luo L, et al. 2016. A novel ranacyclin-like peptide with anti-platelet activity identified from skin secretions of the frog *Amolops loloensis*. *Gene*, **576**(1 Pt 1): 171–175.

Hao X, Yang HL, Wei L, et al. 2012. Amphibian cathelicidin fills the evolutionary gap of cathelicidin in vertebrate. *Amino Acids*, **43**(2): 677–685.

He XQ, Yang SL, Wei L, et al. 2013. Antimicrobial peptide diversity in the skin of the torrent frog, *Amolops jingdongensis*. *Amino Acids*, **44**(2): 481–487.

Herzig V. 2021. Animal venoms-curse or cure?. *Biomedicines*, **9**(4): 413.

Herzig V, Cristofori-Armstrong B, Israel MR, et al. 2020. Animal toxins - Nature's evolutionary-refined toolkit for basic research and drug discovery. *Biochemical Pharmacology*, **181**: 114096.

Hu B, Xu LX, Li Y, et al. 2020. A peptide inhibitor of macrophage migration in atherosclerosis purified from the leech *Whitmania pigra*. *Journal of Ethnopharmacology*, **254**: 112723.

Jerjes-Sánchez C. 2015. Mechanisms of thrombosis. *In*: Jerjes-Sánchez C. Thrombolysis in Pulmonary Embolism. Cham: Springer, 1–17.

Ji MY, Zhu TY, Xing MC, et al. 2019. An antiviral peptide from *Alopecosa nagpag* spider targets NS2B-NS3 protease of flaviviruses. *Toxins*, **11**(10): 584.

Jiang Y, Lin Y, Zheng X. 2014. Clinical applications of insect-derived drugs. *West China Medical Journal*, **29**(2): 391–395.

Jiang YY, Wu Y, Wang T, et al. 2020. Brevinin-1GHd: a novel *Hylarana guentheri* skin secretion-derived Brevinin-1 type peptide with antimicrobial and anticancer therapeutic potential. *Bioscience Reports*, **40**(5): BSR20200019.

Jimenez R, Ikonomopoulou MP, Lopez JA, et al. 2018. Immune drug discovery from venoms. *Toxicon*, **141**: 18–24.

Jin L, Bai XW, Luan N, et al. 2016. A designed tryptophan- and lysine/arginine-rich antimicrobial peptide with therapeutic potential for clinical antibiotic-resistant *Candida albicans* vaginitis. *Journal of Medicinal Chemistry*, **59**(5): 1791–1799.

Johnsen AH. 1994. Identification of cholecystokinin from frog and turtle. Divergence of cholecystokinin and gastrin occurred before the evolution of amphibia. *European Journal of Biochemistry*, **224**(2): 691–702.

King GF. 2011. Venoms as a platform for human drugs: translating toxins into therapeutics. *Expert Opinion on Biological Therapy*, **11**(11): 1469–1484.

King GF, Hardy MC. 2013. Spider-venom peptides: structure, pharmacology, and potential for control of insect pests. *Annual Review of Entomology*, **58**(1): 475–496.

Koh CY, Kini RM. 2008. Anticoagulants from hematophagous animals. *Expert Review of Hematology*, **1**(2): 135–139.

Kong Y, Huang SL, Shao Y, et al. 2013a. Purification and characterization of a novel antithrombotic peptide from *Scolopendra subspinipes mutilans*. *Journal of Ethnopharmacology*, **145**(1): 182–186.

Kong Y, Shao Y, Chen H, et al. 2013b. A novel factor Xa-inhibiting peptide from centipedes venom. *International Journal of Peptide Research and Therapeutics*, **19**(4): 303–311.

Lai R, Liu H, Lee WH, et al. 2002a. A novel proline rich bombesin-related peptide (PR-bombesin) from toad *Bombina maxima*. *Peptides*, **23**(3): 437–442.

Lai R, Liu H, Lee WH, et al. 2002b. Identification and cloning of a trypsin inhibitor from skin secretions of Chinese red-belly toad *Bombina maxima*. *Comparative Biochemistry and Physiology Part B: Biochemistry and Molecular Biology*, **131**(1): 47–53.

Lai R, Liu H, Lee WH, et al. 2002c. An anionic antimicrobial peptide from toad *Bombina maxima*. *Biochemical and Biophysical Research Communications*, **295**(4): 796–799.

Lai R, Liu H, Lee WH, et al. 2003a. Bombinakinin M gene associated peptide, a novel bioactive peptide from skin secretions of the toad *Bombina maxima*. *Peptides*, **24**(2): 199–204.

Lai R, Liu H, Lee WH, et al. 2003b. Two novel Bv8-like peptides from skin secretions of the toad *Bombina maxima*. *Comparative Biochemistry and Physiology Part B: Biochemistry and Molecular Biology*, **134**(3): 509–514.

Lee WH, Du XY, Lu QM, et al. 2003. Stejnulxin, a novel snake C-type lectin-like protein from *Trimeresurus stejnegeri* venom is a potent platelet agonist acting specifically via GPVI. *Thrombosis and Haemostasis*, **90**(4): 662–671.

Lee YS, Lee YJ, Ha IH. 2025. Therapeutic potential of *Scolopendra subspinipes*: a comprehensive scoping review of its bioactive compounds, preclinical pharmacology, and clinical applications. *Toxins*, **17**(5): 229.

Lent CM, Dickinson MH. 1984. Serotonin integrates the feeding-behavior of the medicinal leech. *Journal of Comparative Physiology A*, **154**(4): 457–471.

Li BW, Silva JR, Lu XC, et al. 2019. Molecular game theory for a toxin-dominant food chain model. *National Science Review*, **6**(6): 1191–1200.

Li JX, Liu TG, Xu XQ, et al. 2006a. Amphibian tachykinin precursor. *Biochemical and Biophysical Research Communications*, **350**(4): 983–986.

Li JX, Wu HB, Hong J, et al. 2008a. Odorranalectin is a small peptide lectin with potential for drug delivery and targeting. *PLoS One*, **3**(6): e2381.

Li JX, Wu J, Wang YP, et al. 2008b. A small trypsin inhibitor from the frog of *Odorrana grahami*. *Biochimie*, **90**(9): 1356–1361.

Li JX, Xu XQ, Yu HN, et al. 2006b. Direct antimicrobial activities of PR-bombesin. *Life Sciences*, **78**(17): 1953–1956.

Li JX, Yu HN, Xu XQ, et al. 2007. Multiple bombesin-like peptides with opposite functions from skin of *Odorrana grahami*. *Genomics*, **89**(3): 413–418.

Lian WG, Lian HG, Li Q, et al. 2018. The venom of spider *Haplopelma hainanum* suppresses proliferation and induces apoptosis in hepatic cancer cells by caspase activation in vitro. *Journal of Ethnopharmacology*, **225**: 169–177.

Liang JG, Han YP, Li JX, et al. 2006. A novel bradykinin-like peptide from skin secretions of rufous-spotted torrent frog, *Amolops loloensis*. *Peptides*, **27**(11): 2683–2687.

Lima WG, Maia CQ, de Carvalho TS, et al. 2022. Animal venoms as a source of antiviral peptides active against arboviruses: a systematic review. *Archives of Virology*, **167**(9): 1763–1772.

Lin Y, Chen TB, Zhou M, et al. 2017. Ranatensin-HL: a bombesin-related tridecapeptide from the skin secretion of the broad-folded frog, *Hylarana latouchii*. *Molecules*, **22**(7): 1110.

Liu H, Duan ZL, Tang J, et al. 2014a. A short peptide from frog skin accelerates diabetic wound healing. *The FEBS Journal*, **281**(20): 4633–4643.

Liu H, Mu LX, Tang J, et al. 2014b. A potential wound healing-promoting peptide from frog skin. *The International Journal of Biochemistry & Cell Biology*, **49**: 32–41.

Liu R, Ding YC, Jiang XY, et al. 2024a. Anticoagulant peptides derived from animal-sourced traditional Chinese medicine and their pharmacological effects. *Pharmacological Research-Modern Chinese Medicine*, **13**: 100529.

Liu WH, Chen Y, Bai XW, et al. 2016. Identification and characterization of a novel neuropeptide (neuropeptide Y-HS) from leech salivary gland of *Haemadipsa sylvestris*. *Chinese Journal of Natural Medicines*, **14**(9): 677–682.

Liu XH, Liu R, Wei L, et al. 2011. Two novel antimicrobial peptides from skin secretions of the frog, *Rana nigrovittata*. *Journal of Peptide Science*, **17**(1): 68–72.

Liu XH, Wang YP, Cheng LH, et al. 2007. Isolation and cDNA cloning of cholecystokinin from the skin of *Rana nigrovittata*. *Peptides*, **28**(8): 1540–1544.

Liu XH, You DW, Chen LH, et al. 2008. A novel bradykinin-like peptide from skin secretions of the frog, *Rana nigrovittata*. *Journal of Peptide Science*, **14**(5): 626–630.

Liu XQ, Li S, Feng Y, et al. 2024b. Traditional knowledge of animal-derived medicines used by Gelao community in Northern Guizhou, China. *Journal of Ethnobiology and Ethnomedicine*, **20**(1): 31.

Liu ZC, Zhang R, Zhao F, et al. 2012a. Venomic and transcriptomic analysis of centipede *Scolopendra subspinipes dehaani*. *Journal of Proteome Research*, **11**(12): 6197–6212.

Liu ZH, Zhao Y, Li J, et al. 2012b. The venom of the spider *Macrothele raveni* induces apoptosis in the myelogenous leukemia K562 cell line. *Leukemia Research*, **36**(8): 1063–1066.

Long CB, Liu M, Tian HW, et al. 2020. Potential role of platelet-activating C-type lectin-like proteins in viper envenomation induced thrombotic microangiopathy symptom. *Toxins*, **12**(12): 749.

Lu HP, Chai JW, Xu ZJ, et al. 2024. Cath-KP, a novel peptide derived from frog skin, prevents oxidative stress damage in a Parkinson's disease model. *Zoological Research*, **45**(1): 108–124.

Lu X, Lu D, Scully MF, et al. 2005. Snake venom metalloproteinase containing a disintegrin-like domain, its structure-activity relationships at interacting with integrins. *Current Medicinal Chemistry-Cardiovascular & Hematological Agents*, **3**(3): 249–260.

Lu XY, Ma YF, Wu J, et al. 2008. Two serine protease inhibitors from the skin secretions of the toad, *Bombina microdeladigitora*. *Comparative Biochemistry and Physiology Part B: Biochemistry and Molecular Biology*, **149**(4): 608–612.

Lu Y, Li JX, Yu HN, et al. 2006. Two families of antimicrobial peptides with multiple functions from skin of rufous-spotted torrent frog, *Amolops loloensis*. *Peptides*, **27**(12): 3085–3091.

Luan N, Zhou CL, Li PP, et al. 2017. Joannsin, a novel Kunitz-type FXa inhibitor from the venom of *Prospirobolus joannsi*. *Thrombosis and Haemostasis*, **117**(6): 1031–1039.

Luo CQ, Zhao WJ, Liu S, et al. 2023. Animal-and mineral-based medicines in Gansu-Ningxia-inner Mongolia region, P. R. China: a cross-cultural ethnobiological assessment. *Frontiers in Pharmacology*, **14**: 1295806.

Luo L, Li BW, Wang S, et al. 2018. Centipedes subdue giant prey by blocking KCNQ channels. *Proceedings of the National Academy of Sciences of the United States of America*, **115**(7): 1646–1651.

Marrocco I, Altieri F, Peluso I. 2017. Measurement and clinical significance of biomarkers of oxidative stress in humans. *Oxidative Medicine and Cellular Longevity*, **2017**(1): 6501046.

May RJ, Conlon TP, Erspamer V, et al. 1978. Actions of peptides isolated from amphibian skin on pancreatic acinar cells. *American Journal of Physiology-Endocrinology and Metabolism*, **235**(2): E112–E118.

McLane MA, Sanchez EE, Wong A, et al. 2004. Disintegrins. *Current Drug Targets-Cardiovascular & Hematological Disorders*, **4**(4): 327–355.

Meng P, Huang HG, Wang G, et al. 2016. A novel toxin from *Haplopelma lividum* selectively inhibits the $Na_V1.8$ channel and possesses potent analgesic efficacy. *Toxins*, **9**(1): 7.

Meng P, Wei L, Yang SL, et al. 2012. A novel frog skin peptide containing function to induce muscle relaxation. *Biochimie*, **94**(12): 2508–2513.

Miller C. 1995. The charybdotoxin family of K^+ channel-blocking peptides. *Neuron*, **15**(1): 5–10.

Min GS, Sarkar IN, Siddall ME. 2010. Salivary transcriptome of the North American medicinal leech, *Macrobdella decora*. *The Journal of Parasitology*, **96**(6): 1211–1221.

Moga MA, Dimienescu OG, Arvătescu CA, et al. 2018. Anticancer activity of toxins from bee and snake venom - an overview on ovarian cancer. *Molecules*, **23**(3): 692.

Montinari MR, Minelli S. 2022. From ancient leech to direct thrombin inhibitors and beyond: new from old. *Biomedicine & Pharmacotherapy*, **149**: 112878.

Mu LX, Tang J, Liu H, et al. 2014. A potential wound-healing-promoting peptide from salamander skin. *The FASEB Journal*, **28**(9): 3919–3929.

Mwangi J, Kamau PM, Thuku RC, et al. 2023. Design methods for antimicrobial peptides with improved performance. *Zoological Research*, **44**(6): 1095–1114.

Mwangi J, Tadese DA, Wang Y, et al. 2025. Integrating a cationic backbone with a hydrophobic core: a structure-function strategy for designing self-assembling antimicrobial peptides with enhanced activity. *Zoological Research*, **46**(5): 1203–1218.

Mwangi J, Yin YZ, Wang G, et al. 2019. The antimicrobial peptide ZY4 combats multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* infection. *Proceedings of the National Academy of Sciences of the United States of America*, **116**(52): 26516–26522.

Nielsen KG, Bomgren P, Holmgren S, et al. 1998. Gastrin and cholecystokinin of the bullfrog, *Rana catesbeiana*, have distinct effects on gallbladder motility and gastric acid secretion *in vitro*. *General and Comparative Endocrinology*, **112**(2): 247–254.

Pemberton RW. 1999. Insects and other arthropods used as drugs in Korean traditional medicine. *Journal of Ethnopharmacology*, **65**(3): 207–216.

Pfaff M, McLane MA, Beviglia L, et al. 1994. Comparison of disintegrins with limited variation in the RGD loop in their binding to purified integrins αIIbβ3, αVβ3 and α5β1 and in cell adhesion inhibition. *Cell Adhesion and Communication*, **2**(6): 491–501.

Qi J, Zulfiker AHM, Li C, et al. 2018. The development of toad toxins as potential therapeutic agents. *Toxins*, **10**(8): 336.

Qian ZJ, Jung WK, Kim SK. 2008. Free radical scavenging activity of a novel antioxidative peptide purified from hydrolysate of bullfrog skin, *Rana catesbeiana Shaw*. *Bioresource Technology*, **99**(6): 1690–1698.

Qin CH, Yang XH, Zuo Z, et al. 2021. BmK86-P1, a new degradation peptide with desirable thermostability and Kv1.2 channel-specific activity from traditional Chinese scorpion medicinal material. *Toxins*, **13**(9): 610.

Reiss S, Sieber M, Oberle V, et al. 2006. Inhibition of platelet aggregation by grafting RGD and KGD sequences on the structural scaffold of small disulfide-rich proteins. *Platelets*, **17**(3): 153–157.

Rima M, Alavi Naini SM, Karam M, et al. 2018. Vipers of the middle east: a rich source of bioactive molecules. *Molecules*, **23**(10): 2721.

Rong MQ, Yang SL, Wen B, et al. 2015. Peptidomics combined with cDNA library unravel the diversity of centipede venom. *Journal of Proteomics*, **114**: 28–37.

Saez NJ, Mobli M, Bieri M, et al. 2011. A dynamic pharmacophore drives the interaction between psalmotoxin-1 and the putative drug target acid-sensing ion channel 1a. *Molecular Pharmacology*, **80**(5): 796–808.

Saez NJ, Senff S, Jensen JE, et al. 2010. Spider-venom peptides as therapeutics. *Toxins*, **2**(12): 2851–2871.

Samy RP, Foo SL, Franco OL, et al. 2017. Identification of natural peptides as a new class of antimalarial drugs by *in silico* approaches. *Frontiers in Bioscience (Scholar Edition)*, **9**(1): 88–110.

Scarborough RM, Rose JW, Naughton MA, et al. 1993. Characterization of the integrin specificities of disintegrins isolated from American pit viper venoms. *The Journal of Biological Chemistry*, **268**(2): 1058–1065.

Serna N, Sánchez-García L, Unzueta U, et al. 2018. Protein-based therapeutic killing for cancer therapies. *Trends in Biotechnology*, **36**(3): 318–335.

Shi ZF, Song TB, Wan Y, et al. 2017. A systematic review and meta-analysis of traditional insect Chinese medicines combined chemotherapy for non-surgical hepatocellular carcinoma therapy. *Scientific Reports*, **7**(1): 4355.

Sig AK, Guney M, Uskudar Guclu A, et al. 2017. Medicinal leech therapy-an overall perspective. *Integrative Medicine Research*, **6**(4): 337–343.

Silva JC, Neto LM, Neves RC, et al. 2017. Evaluation of the antimicrobial activity of the mastoparan Polybia-MPII isolated from venom of the social wasp *Pseudopolybia vespiceps testacea* (Vespidae, Hymenoptera). *International Journal of Antimicrobial Agents*, **49**(2): 167–175.

Soorki MN. 2025. In silico antiviral effect assessment of some venom gland peptides from *Odontobuthus doriae* scorpion against SARS-CoV-2. *Toxicon*, **255**: 108229.

Sun ZJ. 2015. Earthworm as a biopharmaceutical: from traditional to precise. *European Journal of BioMedical Research*, **1**(2): 28–35.

Swartz KJ. 2007. Tarantula toxins interacting with voltage sensors in potassium channels. *Toxicon*, **49**(2): 213–230.

Swartz KJ, MacKinnon R. 1997a. Hanatoxin modifies the gating of a voltage-dependent K^+ channel through multiple binding sites. *Neuron*, **18**(4): 665–673.

Swartz KJ, MacKinnon R. 1997b. Mapping the receptor site for hanatoxin, a gating modifier of voltage-dependent K^+ channels. *Neuron*, **18**(4): 675–682.

Tang XP, Chen MR, Duan ZL, et al. 2018. Isolation and characterization of poecistasin, an anti-thrombotic antistasin-type serine protease inhibitor from leech *Poecilobdella manillensis*. *Toxins*, **10**(11): 429.

Tian HW, Liu M, Li JM, et al. 2020. Snake C-type lectins potentially contribute to the prey immobilization in *Protobothrops mucrosquamatus* and *Trimeresurus stejnegeri* venoms. *Toxins*, **12**(2): 105.

Undheim EAB, Jenner RA, King GF. 2016. Centipede venoms as a source of drug leads. *Expert Opinion on Drug Discovery*, **11**(12): 1139–1149.

Wali A, Wubulikasimu A, Mirzaakhmedov S, et al. 2019. Optimization of scorpion protein extraction and characterization of the proteins' functional properties. *Molecules*, **24**(22): 4103.

Wang AL, Wang JY, Hong J, et al. 2008a. A novel family of antimicrobial peptides from the skin of *Amolops loloensis*. *Biochimie*, **90**(6): 863–867.

Wang G, Long CB, Liu WH, et al. 2018. Novel sodium channel inhibitor from leeches. *Frontiers in Pharmacology*, **9**: 186.

Wang GX, Wang Y, Ma DY, et al. 2013. Five novel antimicrobial peptides from the Kuhl's wart frog skin secretions, *Limnonectes kuhlii*. *Molecular Biology Reports*, **40**(2): 1097–1102.

Wang MJ, Wang Y, Wang AL, et al. 2010. Five novel antimicrobial peptides

from skin secretions of the frog, *Amolops loloensis*. *Comparative Biochemistry and Physiology Part B: Biochemistry and Molecular Biology*, **155**(1): 72–76.

Wang XL, Umetsu Y, Gao B, et al. 2015a. Mesomartoxin, a new K_v1.2-selective scorpion toxin interacting with the channel selectivity filter. *Biochemical Pharmacology*, **93**(2): 232–239.

Wang YP, Hong J, Liu XH, et al. 2008b. Snake cathelicidin from *Bungarus fasciatus* is a potent peptide antibiotics. *PLoS One*, **3**(9): e3217.

Wang YP, Zhang ZY, Chen LL, et al. 2011. Cathelicidin-BF, a snake cathelicidin-derived antimicrobial peptide, could be an excellent therapeutic agent for acne vulgaris. *PLoS One*, **6**(7): e22120.

Wang YW, Tan JM, Du CW, et al. 2015b. A novel trypsin inhibitor-like cysteine-rich peptide from the frog *Lepidobatrachus laevis* containing proteinase-inhibiting activity. *Natural Products and Bioprospecting*, **5**(4): 209–214.

Wei L, Dong L, Zhao TY, et al. 2011. Analgesic and anti-inflammatory effects of the amphibian neurotoxin, anntoxin. *Biochimie*, **93**(6): 995–1000.

Wei L, Yang JJ, He XQ, et al. 2013. Structure and function of a potent lipopolysaccharide-binding antimicrobial and anti-inflammatory peptide. *Journal of Medicinal Chemistry*, **56**(9): 3546–3556.

Wu SH, Zhou YY, Wang Y, et al. 2024. Therapeutic potentials of medicinal leech in Chinese medicine. *The American Journal of Chinese Medicine*, **52**(4): 1027–1051.

Xia ZQ, Wang HJ, Chen WL, et al. 2024. Scorpion venom antimicrobial peptide derivative BmKn2-T5 inhibits Enterovirus 71 in the early stages of the viral life cycle *in vitro*. *Biomolecules*, **14**(5): 545.

Xing MC, Ji MY, Hu JM, et al. 2020. Snake Cathelicidin derived peptide inhibits Zika virus infection. *Frontiers in Microbiology*, **11**: 1871.

Xu C, Wang YF, Tu Q, et al. 2019. Targeting surface nucleolin induces autophagy-dependent cell death in pancreatic cancer via AMPK activation. *Oncogene*, **38**(11): 1832–1844.

Xu XQ, Lai R. 2015. The chemistry and biological activities of peptides from amphibian skin secretions. *Chemical Reviews*, **115**(4): 1760–1846.

Xu XQ, Li JX, Han YP, et al. 2006a. Two antimicrobial peptides from skin secretions of *Rana grahami*. *Toxicon*, **47**(4): 459–464.

Xu XQ, Li JX, Lu QM, et al. 2006b. Two families of antimicrobial peptides from wasp (*Vespa magnifica*) venom. *Toxicon*, **47**(2): 249–253.

Xu XQ, Yang HL, Ma DY, et al. 2008. Toward an understanding of the molecular mechanism for successful blood feeding by coupling proteomics analysis with pharmacological testing of horsefly salivary glands. *Molecular & Cellular Proteomics*, **7**(3): 582–590.

Yacoub T, Rima M, Karam M, et al. 2020. Antimicrobials from venomous animals: an overview. *Molecules*, **25**(10): 2402.

Yan HL, Liu YY, Tang J, et al. 2013. A novel antimicrobial peptide from skin secretions of the tree frog *Theloderma kwangsiensis*. *Zoological Science*, **30**(9): 704–709.

Yan HL, Wei L, He XQ, et al. 2012. A novel myotropic peptide from the skin secretions of the tree frog, *Polypedates pingbianensis*. *Biochimie*, **94**(8): 1718–1723.

Yan XW, Feng H, Yu HN, et al. 2008. An immunoregulatory peptide from salivary glands of the horsefly, *Hybomitra atriperoides*. *Developmental & Comparative Immunology*, **32**(10): 1242–1247.

Yang F, Wang DY, Tong YJ, et al. 2019. Thermostable potassium channel-inhibiting neurotoxins in processed scorpion medicinal material revealed by proteomic analysis: implications of its pharmaceutical basis in traditional Chinese medicine. *Journal of Proteomics*, **206**: 103435.

Yang HL, Xu XQ, Ma DY, et al. 2008. A phospholipase A1 platelet activator from the wasp venom of *Vespa magnifica* (Smith). *Toxicon*, **51**(2): 289–296.

Yang SL, Liu ZH, Xiao Y, et al. 2012. Chemical punch packed in venoms makes centipedes excellent predators. *Molecular & Cellular Proteomics*, **11**(9): 640–650.

Yang SL, Wang YF, Wang L, et al. 2020. Target switch of centipede toxins for antagonistic switch. *Science Advances*, **6**(32): eabb5734.

Yang SL, Xiao Y, Kang D, et al. 2013. Discovery of a selective Na_V1.7 inhibitor from centipede venom with analgesic efficacy exceeding morphine in rodent pain models. *Proceedings of the National Academy of Sciences of the United States of America*, **110**(43): 17534–17539.

Yang SL, Yang F, Wei NN, et al. 2015. A pain-inducing centipede toxin targets the heat activation machinery of nociceptor TRPV1. *Nature Communications*, **6**(1): 8297.

Yang SL, Yang F, Zhang B, et al. 2017. A bimodal activation mechanism underlies scorpion toxin-induced pain. *Science Advances*, **3**(8): e1700810.

Yin SJ, Yi H, Ma YB, et al. 2008. Characterization of a new Kv1.3 channel-specific blocker, J123, from the scorpion *Buthus martensii* Karsch. *Peptides*, **29**(9): 1514–1520.

Yu HN, Qiao X, Gao JX, et al. 2015. Identification and characterization of novel antioxidant peptides involved in redox homeostasis of frog, *Limnonectes fragilis*. *Protein & Peptide Letters*, **22**(9): 776–784.

Zamponi GW. 2016. Targeting voltage-gated calcium channels in neurological and psychiatric diseases. *Nature Reviews Drug discovery*, **15**(1): 19–34.

Zeng BS, Chai JW, Deng ZH, et al. 2018. Functional characterization of a novel lipopolysaccharide-binding antimicrobial and anti-inflammatory peptide in vitro and in vivo. *Journal of Medicinal Chemistry*, **61**(23): 10709–10723.

Zeng XC, Wang SX, Zhu Y, et al. 2004. Identification and functional characterization of novel scorpion venom peptides with no disulfide bridge from *Buthus martensii* Karsch. *Peptides*, **25**(2): 143–150.

Zhong SR, Wu JB, Cui YP, et al. 2015. Vascular endothelial growth factor from *Trimeresurus jerdonii* venom specifically binds to VEGFR-2. *Biochimie*, **116**: 1–7.

Zhou C, Wang ZM, Peng X, et al. 2018. Discovery of two bombinin peptides with antimicrobial and anticancer activities from the skin secretion of Oriental fire-bellied toad, *Bombina orientalis*. *Chemical Biology & Drug Design*, **91**(1): 50–61.

Zhou ZH, Yang HL, Xu XQ, et al. 2006. The first report of kininogen from invertebrates. *Biochemical and Biophysical Research Communications*, **347**(4): 1099–1102.

Zhu YY, Zhao LM, Jia XY, et al. 2025. Amphibians as a source of bioactive antioxidant peptides: emerging insights and therapeutic potential. *Zoological Research*, **46**(5): 1219–1243.