Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423)

Volume 10 Issue 1 January 2026

Review Article

Frog Toxin Types: Their Biological Effects and Therapeutic Uses

Arunima Yadav and Ravi Kant Upadhyay*

Department of Zoology, D D U Gorakhpur University, Gorakhpur, 273009. U.P. India

***Corresponding Author:** Ravi Kant Upadhyay, Department of Zoology, D D U Gorakhpur University, Gorakhpur, 273009. U.P. India.

DOI: 10.31080/ASPS.2025.10.1246

Received: December 01, 2025

Published: December 19, 2025

Abstract

This article describes various toxins derived from skin glands of various frog species, along with their pharmacological and therapeutic uses. Most of these toxic compounds from skin glands, are used to protect against harmful microorganisms, parasites, and predators. These can be used as diagnostic tools, mainly experimental molecules to validate postulated therapeutic targets. This article discusses various toxins secreted from frog skin glands, primarily examining their antimicrobial, insulinotropic, antitrypanosomal, hemolytic, wound-healing, anti-HIV, and insecticidal properties. Bufadienolides exhibited cytotoxic, antitumor, anticancer, anti-inflammatory, antimicrobial, and analgesic activities. These are also used to create drug libraries, prototypes for drug design, cosmeceuticals, therapeutic agents and traditional medicines. This review suggests that the use of frog toxins may contribute to the development of novel therapeutic molecules for managing infectious diseases.

Keywords: Bufadienolides; Cytotoxic; Antitumor; Antimicrobial and Analgesic Activity

Introduction

Amphibians have skin that is heavily packed with glands that produce toxins and mucus. These secretions show a wide range of harmful effects on human health. These have adverse physiological effects due to toxic action on various bodily tissue systems that give rise to serious health issues. Thus, envenomation or direct exposure to these toxins or poisons can cause significant economic problems and health risks for humans, their pets, and wild animals. Among vertebrates, amphibians secrete a wide variety of chemicals from their skin glands as a defence against predators, parasites, and pathogens. These defensive chemicals are produced endogenously through biosynthesis, whereas poison frogs sequester lipophilic alkaloids from their diet. Several frog families produce skin-secreted peptides [1]. These skin poisons are composed of bioactive peptides for defence against pathogens, parasites and predators. Bufo toads, Colorado River toad, Giant marine toad, Sonoran Desert toad (*Bufo alvarius*), and cane toad (*Rhinella marina*) possess poison glands on their backs and behind their eyes. These produce a toxic fluid that contains important poisonous components, including digoxin, a cardioactive steroid, Catecholamines, and tryptamines. These impose life-threatening toxicity and hallucinogenic effects. Alkaloid diversity is highly variable among adult poison frogs.

Anurans belonging to Dendrobatidae secrete several toxins in their skin [2]. *Rana catesbeiana*, a ranid frog also secretes bombesin-like peptide [3]. The ranid frogs also have yielded two new homologous bombesin peptides, bombesin-OS and bombesin-PE [4]. These peptides penetrate cells [5]. Similarly an unique vasoactive BPP was discovered in the cutaneous secretion of the frog *Brachycephalus ephippium* [6]. The skin secretion of the *A. loloensis* frog contains amolopinis [7]. The skin secretions of the European Edible Frog (*Pelophylax kl. esculentus*) and the Chinese Piebald Odorous Frog (*Odorrana schmackeri*) have also been found to contain a1 3 peptide [4]. Similarly, a novel vasoactive BPP isolated from the skin secretion of the frog *Brachycephalus ephippium* [6]. Amolopinis occurs in the skin secretions of the frog *A. loloensis* [7]. Similarly, a peptide has been identified in the skin secretions of the Chinese piebald odorous frog (*Odorrana schmacker*) and the European edible frog (*Pelophylax kl. esculentus*) [4]. A novel myotropic tryptophyllin-3 peptide, named Baltikinin, has been isolated from the skin secretion of the purple-sided leaf frog (*Phyllomedusa baltea*) [8]. *Argenteohyla siemersi* (red-spotted Argentina frog) belong to the Hylidae family and makes a complex combination of anti-predator defense mechanisms by using highly lethal skin secretion [9].

Toads, which belong to the family Bufonidae, produce bioactive substances in secretions from specialised skin macroglands. Bufonidae, better known as true toads, members of this family contain bufadienolides in their venom [10]. The frog *Amolopsloloensis* secretes antimicrobial peptides, which are proline-rich peptides similar to bradykinin-like peptides and algesic peptides. The Angiotensin-Converting Enzyme (ACE) is inhibited by these. The blunt posterior end of the caecilian *Siphonops annulatus*, which has an internalised mega gland of poison glands in the dermis, may function as a chemical defensive mechanism or prevent tunnel penetration [11]. The majority of these bufadienolides have cytotoxic and anticancer properties against kidney Vero epithelial cells [12]. These serve as protective compounds and have been shown to vary greatly among adult poison frogs [10]. As a traditional therapy for infectious disorders, these substances were discovered to be effective against microbial pathogens [12].

Amphibian skin poisonous secretions play fundamental role in chemical defense against predators and microorganisms—These skin glands. During the breeding season, sexually dimorphic glands become active, and males make calls to attract females [13]. These assist the animal in intraspecific chemical communication during mating [14]. In anurans, reproduction is associated with skin glands. The Brazilian microhylid *Dermatonotus muelleri* (Muller's termite frog) is known for its highly toxic skin secretions [14]. The skin secretion of the *A. loloensis* frog was shown to contain a novel insulinotropic peptide called amolopin [7]. Common toads, including the natterjack toad (*epidalea calamita*), produce bufadienolides [6]. Secretions of the post-axillary gland are proteinaceous sexual pheromones that are believed to attract females during male calling intervals [13].

Many frog species secrete toxic compounds from their skin glands, which are bioactive peptides serving to protect against harmful microorganisms, parasites, and predators. Frog toxins have numerous potential therapeutic applications [15]. These can be used as diagnostic tools, mainly experimental molecules to validate postulated therapeutic targets. These are also used to create drug libraries, prototypes for drug design, cosmeceuticals, and therapeutic agents. The creation of toxin-based products and the search for new drugs could both benefit from these toxins [16]. This review describes toxins from the venoms of various frog species comprising different classes of molecules with diverse pharmacological activities. This also highlights bioactive species and their various biological activities, including anti-trypanosomal, anticancer, antidiabetic, anti-inflammatory, anti-HIV, and insecticidal properties.

Source of data

This comprehensive review examines frog toxins, bioactive natural products, and their pharmacological and therapeutic applications. To gather relevant information, various databases were searched using specific keywords such as toxin types, antimicrobial peptides, insulinotropic activity, bufadienolides, cytotoxicity, antitumor effects, hemolytic activity, and wound healing properties. Emphasis was placed on retrieving articles related to frog-derived

toxins and their medicinal, pharmacological, and therapeutic uses, including treatments for skin cancer, as well as their anti-inflammatory, immunomodulatory, and anticancer activities. Additional references were obtained by reviewing citations within existing studies. Both individual and combined search terms were employed to ensure a thorough literature review. To incorporate recent developments and update the information, research articles, books, conference proceedings, and reports from public health organizations were selected and compiled. Searches were conducted across platforms such as Web of Science, PubMed, PMC, and Google. Using this standard approach, key discoveries and findings were identified and summarized in the final review.

Toxin types

Frog toxins contains varieties of compounds, including alkaloids, amines, peptides, proteins, and steroids. The most well-known are lipid-soluble alkaloids, such as batrachotoxins, histrionicotoxins, pumiliotoxins, and gephyrotoxins. Frog poison glands also secrete antimicrobial peptides, hormones, and enzymes. Alkaloids bind to nicotinic acetylcholine receptors all over the body and cause convulsions, paralysis and then death. Toxins from venoms of various frog species comprise different classes of molecules with wide-ranging pharmacological activities. Toad *Bufo marinus* venom possesses a cardiac glycoside, which has multiple adverse effects on human health.

Bufadienolides

Bufadienolides are cardiotonic steroids compounds derived from the venom of toads (family Bufonidae) (Figure 1). Bufadienolides are C-24 steroids distinguished by a six-membered lactone ring containing two double bonds at the C-17 position. They are known for their cardioactive and toxic properties, as they inhibit the sodium-potassium pump, a mechanism similar to that of other cardiac glycosides. These compounds have potential medicinal uses, including anti-cancer, anti-inflammatory, anti-leishmanial, anti-trypanosomal, antithrombotic, and antiviral effects. They can increase sodium excretion, cause vasoconstriction, and strengthen heart muscle contractions (inotropic effect). They are toxic and can cause severe cardiac issues, including bradycardia and cardiac arrest. These are potent inhibitors of Na^+/K^+ ATPase with excellent anti-inflammatory activity. However, the severe side effects triggered by the unbiased inhibition of whole-body cells, specifically the α1-subtype of Na+/K+ ATPase [4]. The bufadienolides are derived from toads and belong to the C-24 steroid family. These are further derived from toads [4]. Bufotalin, which originates from the toad venom family, is a toxic and pharmacologically valuable biotoxin used in traditional medicine and holds significant promise in modern drug development [18] (Table 1).

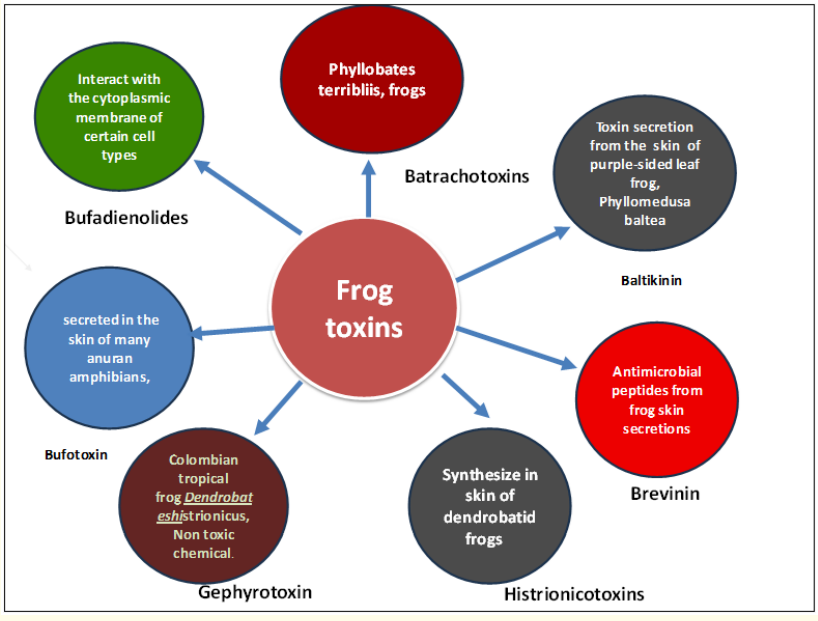

Figure 1: Shows the major toxin peptides isolated from different frog species.

Table 1: Presents the major toxin peptides isolated from amphibian species, along with their corresponding biological effects.

Name of species	Toxin	Type	Effect	References
Toad—Epidalea calamita	bufotoxin	Skin of natterjack	Skin toxicity.	[6]
Phyllomedusa baltea	Baltikinin	Myotropic Tryptophyllin-3 Peptide	Arterial smooth muscle relaxation activity	[9]
Dendrobates tinctorius	Pumiliotoxin (PTX)	Decahydroquinolines (DHQs), izidines, coccinellines, and spiropyrrolizidine alkaloids.	PTX interferes with muscle contraction by affecting calcium channels, causing locomotor difficulties, colonic convulsions, paralysis	[2,53]
Rhinella alata	Bufadienolides	Polyhydroxy steroids	Work against trypomastigotes of T. Cruzi. Anti-inflammatory activity.	[12]
Pelophylax kl esculentus	Bombesin PE	4-amino acid peptide	Effects on smooth muscle were determined in the bladder, uterus, and ileum	[17]
Parotoid glands of true toads *Rhinella marinaRhaeboquattus Bufo melanosticus Bufo bufo*	Bufotalin	bufadienolide steroid	apoptosis induction, cell cycle arrest, endoplasmic reticulum stress activation, and inhibition of metastasis	[18]
Dendrobates histrionicus	Histrionicotoxins	Spiropiperidine ring system, alkene groups in the side chains, and an alcohol group (hydroxyl group) on the ring	Neurotoxic effects	[19]
Odorrana schmacker	Bombesin OS	Odorranain-BLP-5	The effects smooth muscle inside the bladder, uterus, and ileum.	[29]
Phyllobates terriblis	Batrachotoxins	BTX has a rigid steroidal core structure with a tertiary amine	Targetsvoltage-gated Na^+ channel, essential for the generation and propagation of action potentials in excitable membranes	[21]
Pelophylax nigromaculatus	The Brevinin peptides	antimicrobial peptides	Anti-tumour activity through lysosome-mitochondrial death pathway.	[26]
Bufo bufo	Bufadienolide toxins.	C-24 steroid	Antitumor and anti-inflammatory activity	[17]
Ranid frogs, Ranidae, Hylidae and Bombinatorida	antimicrobial peptide	Short amino acid peptide	Active against bacteria, fungi, viruses and protozoans	[30]
Physalaemus nattereri	Anticancer compounds	antimicrobial and antitumoral compounds	Cytotoxiceffects in skin cancer cells, antiproliferative effects on *in vitro* Melanoma Cells.	[34]
Cane toad (*Rhinella marina*	Cardenolide aglycones	C-3 glycosides and Cardenolide aglycones	Exhibit Na^+/K^+ **ATPase inhibitory activity**	[38]
Bufo marinus, the cane toad	Bufagin	Steroid $C_{24}H_{34}O_5$	Analgesic effects and anticancer activity	[54]

Rana pipiens	digoxin	cardiac glycoside drug class	Induce lethargy, confusion and gastro-intestinal symptoms (anorexia, nausea, vomiting, diarrhoea and abdominal pain).	[55]
Skin venom gland of the toad	Resibufogenin	C-24 steroids (α -pyrone ring)	Pharmacologicand toxicologic effects, triggered arrhythmias both in cardiac fiber *in vitro* and in beating heart *in vivo* at the high concentrations	[57]
Skin secretion of three arboreal amphibian species	Bufotenin	Type A (BTX-A)	Act on potent hallucinogenic factor, showing similar activity to LSD upon interaction with the 5HT2 human receptor	[58]
True toads	Cardenolides	Cardioactive steroid	Effects against congestive heart failure and atrial fibrillation.	[59]
True toads	Arenobufagin	Bufadienolidessteroides	Cardiotonic, analgesic and anti-tumor effect	[60]

Batrachotoxins

Batrachotoxin is a potent, steroidal alkaloid neurotoxin found in certain poison dart frogs. The batrachotoxin is derived from 7,8-dihydrobatrachotoxinin A, which is an intermediate (Figure 1). The molecule contains seven asymmetric carbon atoms. The cis A/B and C/D ring junctions cause the molecule to assume the characteristic shape of cardioactive steroids. These toxins are isolated from poison dart frogs. Colombian arrow poison frog with *P. terriblis* Voltage-gated Na+ channels are impacted by *Phyllobates aurotaenia* [19], which keeps them open. BTX affects excitable membranes' voltage-sensitive sodium channels [20]. It is extremely poisonous and causes irreversible depolarisation, paralysis, cardiac arrhythmias, and death by attaching itself to voltage-gated sodium channels and blocking their closure.. Frogs use these toxins to protect themselves from predators. Single substitution in five amino acid in the muscle Na+ channel of *P. terribilis* affects channel binding [21] (Table 1).

Baltikinin

The epidermis of the purple-sided leaf frog, *Phyllomedus baltea*, contains a new tryptophyllin-3 peptide. . The mature peptide primary structure of this N-terminally pyroglutamylated peptide is pGluDKPFGPPPIYPV. With an EC50 of 7.2 nM. baltikinin is a short tryptophyllin peptide, it was discovered to relax the smooth muscle of the rat tail artery (Figure 1). This demonstrates the relaxing activity of arterial smooth muscle [8] (Table 1).

Pumiliotoxin

Pumiliotoxin denotes a class of poisonous alkaloids present within the skin of poison dart frogs. Pumiliotoxin A and pumiliotoxin B represent fat-soluble alkaloids; these stand as principal toxic alkaloids procured from skin extracts originating from the diminutive dendrobatid frog known as *Dendrobates pumilio*, encountered frequently on Isla Bastimentos, Panama [50] (Figure 1). These alkaloids possess substantial fat-soluble attributes. The pumiliotoxins, composing a collection of alkyl and hydroxyl-substituted indolizidine alkaloids, are set apart from the majority of alkaloids originating from arthropods due to their characteristic highly branched carbon frameworks. All species across the Phyllobates and Dendrobates genera contain these particular toxins.Pumiliotoxins A and B are more potent than those of group C. This group of toxins affects the transport of calcium ions in calcium- and sodium-

dependent processes within nerve and skeletal muscles [22] [23]. Pumiliotoxins are often 100 to 1000 times less toxic than their batrachotoxin counterparts. Pumiliotoxin acts as a stimulant (like PTX-B) and others as depressants (like PTX 251D) [24] (Table 1).

Bufotoxin

Bufotoxins are secreted by the parotid glands of anuran amphibians, mainly toads, which belong to the Bufonidaefamily (Figure 1). These glands also secrete bufagin, bufotenine and serotonin that act as a vasoconstrictor. Chemically, these are steroid lactones or substituted tryptamines [25]. Bufotoxins act on the cardiovascular system by inhibiting the Na+/K+ ATPase pumps, similar to digitalis, which can lead to cardiac effects such as ventricular fibrillation. Bufotoxins have a local anaesthetic effect and the ability to inhibit cancer cell proliferation in models of leukaemia, melanoma, and prostate cancer. In low doses, certain bufagins (a type of bufotoxin) are used in traditional medicine. In low doses, certain bufagins (a type of bufotoxin) are used in traditional Chinese medicine to treat conditions such as atrial fibrillation, much like digoxin is used in Western medicine. Like digitalis, bufotoxins inhibit the sodium-potassium pump [25,48] (Table 1).

Bufadienolide toxins

Bufadienolides have been extracted from species belonging to the genera Bufo, Bufotes, Duttaphrynus, and Rhinella [12] (Figure 1). Bufadienolide is a secondary metabolite belonging to the class of steroids. This is an important member of the C-24 steroid family, characterised by an α-pyrone positioned at C-17. As the predominantly active constituent in traditional. As the main active ingredient in traditional Chinese medicine, bufadienolide has been utilized for the treatment of various conditions. Bufadienolides exhibited both antimicrobial and cytotoxic activities against cancer cell lines by activating the lysosomal-mitochondrial death pathway [26]. These are potent inhibitors of Na^+/K^+ ATPase with excellent anti-inflammatory activity (Table 1).

Bradykinin-related peptides

Bradykinin-related peptides with therapeutic significance have been identified from amphibians.

Amphibian species skin possesses hundreds of bioactive peptides, including bradykinin-related peptides (BRPs). They belong to the families Ascaphidae (1 species), Bombinatoridae (3 species), Hylidae (9 species) and Ranidae (25 species). It is essential to investigate the biotechnological, physiological, and pharmacological properties of bioactive rich peptides extracted from the skin secretions of amphibians. In particular, volatile substances present in the skin of the treefrog known as *Hypsiboas pulchellus* (belonging to the Amphibia, Anura, and Hylidae groups) originate from the scented secretions found inside anuran serous glands. Serous glands, also referred to as granular or venomous glands, are found in the skin of nearly every species of adult amphibians. Such volatile substances are scented and possess defensive roles. *Dendrobates tinctorius* secretions contain pumiliotoxin. Dendrobatidis skin, which interferes with muscle contraction and causes locomotor difficulties [2] (Table 1) (Figure 1).

Bombesin-OS and Bombesin-PE

Two new bombesin-like peptides, bombesin-OS and bombesin-PE [29] were discovered from *Odorrana schmackeri* and *Pelophylax kl esculentus*, respectively, and were found in a variety of amphibian skin secretions. Bombesin-OS's precursor is homologous to odorranain-BLP-5, a bombesin-like peptide, and bombesin-PE is a member of the theranatensin subfamily. Amphibian-derived bombesin is a cell-penetrating short polypeptide that can translocate across plasma membranes, interact selectively with the cytoplasmic membrane of particular cell types, and accumulate in the cytoplasm of cells, organelles (such as the nucleus and mitochondria), and other subcellular compartments. To improve cell selectivity, bioavailability, and a variety of target applications, these venom CPPs have undergone structural or chemical modification [5]. BothbombesinOS and bombesin-PE exhibited similar contractile activity on ileum smooth muscle and uterine smooth muscle, but showed higher potency on bladder smooth muscle. These substances might offer a new treatment approach for muscle-related issues and potentially be developed into medications suitable for use in humans (Table 1) (Figure 1).

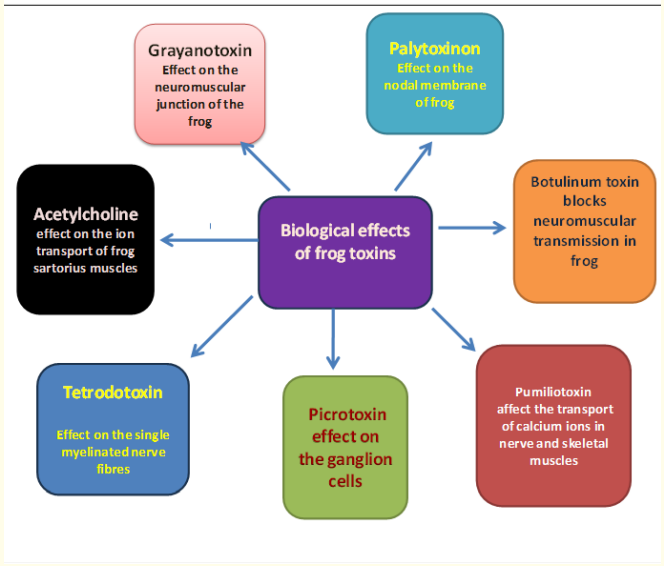

Figure 2: Shows the biological effects of major toxin peptides isolated from different frog species.

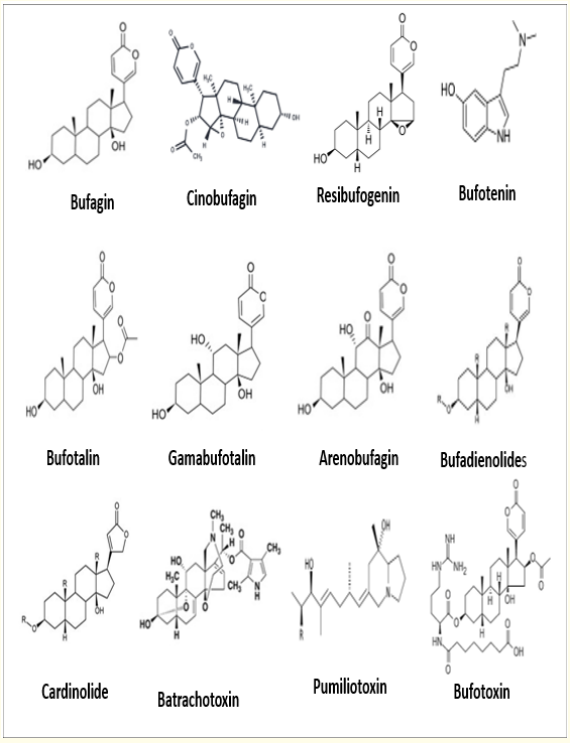

Figure 3: Shows the chemical structure of various frog toxins isolated from different species.

Bombesin-related peptides

Peptides linked to bombesin constitute a family of peptides extracted from Bombina skin, with the original version initially identified in amphibian skin, displaying a diverse array of biological functions. Bombesin-resembling peptide sourced from *Rana catesbeiana* at both the nucleotide and amino acid levels, potentially offering insight for the taxonomic categorization of ranid frogs moving forward [3] (Figure1). Ranatensin-HL originates from the skin secretion of the broad-folded frog, known as *Hylaranala touchii*. It is composed of 13 amino acid residues, pGlu-RAGNQWAIGHFM-NH2, and resembles an N-terminally extended form of Xenopus neuromedin B. Ranatensin-HL and its C-terminal decapeptide. The bombesin-like peptides, bombesin-OS and bombesin-PE, were isolated from *Odorrana schmacker* and *Pelophylax kl*. esculentus, ranid frogs, also in the provision of new drugs for human health [4].

Pharmacological and therapeutic uses

Antimicrobial activity

Various types of frogs generate a wide variety of chemical substances from their skin, and these substances possess significant possibilities in the field of biomedicine. Included within these substances are antimicrobial peptides (AMPs), which represent effector molecules with multiple functions that have been extracted from anurans [30]. The specific AMPs that were recognized came from the family of wild green paddy frogs and include Hylaranaerythraeaesculentin-1, esculentin-2, brevinin-1, and frenatin-4 [31]. These show direct antimicrobial activities with signalling or immunomodulatory functions [31]. These bioactive compounds have great biomedical importance. These studies showed that secretion extracts exhibit inhibitory activity *in vitro* against clinical isolates of bacteria, including resistant and standard strains, as well as fungal and parasitic human pathogens [31]. AMP precursors have been isolated from Ranidae, Hylidae, and Bombinatoridae [30]. Antimicrobial peptides were successfully extracted from the skin's secretions of the *Amolops loloensis* frog (Figure 2).

Insulinotropic activity

Amphibian skin secretions harbor toxin peptides that exhibit distinct blood sugar-lowering properties. Many of these peptides

share cationic and amphipathic structural similarities and appear to possess cell-penetrating abilities. These compounds showed insulinotropic action and regulated the blood glucose levels in animal models. Anti-diabetic peptides originating from toxins represent encouraging potential medications for addressing type 2 diabetes [33].

A previously unidentified peptide that stimulates insulin production, known as amolopin, was discovered within the skin secretions of the *A. loloensis* frog [7] (Figure 2).

Anti-trypanosomal activity

Among bufadienolides, an arginyl-diacid attached to C-3, and a hydroxyl group at C-14 was found active against trypanosomiasis [13]. Bufadienolides showed cytotoxic activity against epithelial kidney Vero cells; however, bufagins (2 and 10) displayed low mammalian cytotoxicity [12] (Figure 2).

Anticancer

The skin of amphibians has a wealth of bioactive compounds, such as peptides, proteins, alcohols, biogenic amines, esters, and alkaloids, that are crucial for different processes, including anticancer, immunomodulatory, and anti-inflammatory activities. Anuran secretions are rich sources of bioactive molecules, which have shown potent antimicrobial and antitumoral activity. *Physalaemus nattereri*, a frog belonging to the Leptodactylidae family within the Anura order, produces a skin secretion that has been shown to hold considerable promise in the treatment of skin cancer cells. Its crude secretion shows cytotoxic Activity and antiproliferative effects on *in vitro* Melanoma Cells. These peptides, found in the secretome, are effective against murine B16F10 tumour cells [34]. These naturally occurring anticancer peptides sourced from amphibians demonstrate substantial efficacy [5]. *Argenteohyla siemersi*, commonly known as the red-spotted Argentina frog, constitutes a specific type of casque-headed tree frog.

This frog is taxonomically classified within the Hylidae family. Certain peptides are secreted by the skin of *A. siemersi* and are essential to the protective systems observed in casque-headed frogs [9]. This secretion exhibited hemolytic and phospholipase A2 activities, as well as dose-dependent cytotoxicity in cultured C2C12 myoblasts. Theparotid glands found in agricultural habitats had smaller parotoids and secrete lower bufotoxin concentrations [36]. Anthropogenic activities influence anti-predatory chemical defence [36]. The *Odorrana schmackeri* and *Pelophylaxkl. esculentus* ranid frogs have great therapeutic importance [37] (Figure 2).

Protective effects

Animals that ingest toxins can become unpalatable and even toxic to predators and parasites through the process of toxin sequestration. Bufagenins found in the cane toad (*Rhinella marina*) attract older conspecific larvae, which are highly cannibalistic and can consume an entire clutch. Cardenolide aglycones (e.g., digitoxigenin) were active attractors, whereas C-3 glycosides (e.g., digoxin, ouabain) were far less effective [38]. Similarly, marinobufagin was more effective than marino bufotoxin [38]. Passive toxin accumulation that accompanies increased toxin intake may underlie the early origins of chemical defence [39]. Toxins also attract palatable prey and assist the animal in feeding on it [40]. The tetrodotoxin, procaine, and manganese ions affect the "Ca spike" of the barnacle fibre (Figure 2).

Hemolytic effects

The frog Kaloula pulchra Hainanensis skin secretions showed hemolytic activity against human, cattle, rabbit, and chicken erythrocytes. These skin secretions of *K. pulchra hainana* induce a pore-forming mechanism to form pores with a diameter of 1.36-2.0 nm rather than causing oxidative damage to the erythrocyte membrane [41]. The bullfrog (*Rana catesbeiana)* enzymatically dissociated hair cells; both a calcium-activated K+ (KCa) current and a voltage-dependent K+ (KV) current contributed to the oscillatory responses of hair cells in the semi-intact preparation [42]. Frog skin synthesises diverse bioactive components, which are used in ethnoveterinary medicine and Ethnomedicine [6]. These also act as defence chemicals. Defensive chemicals were unrelated to sex, independent of size [10] (Figure 2).

Wound healing activity

Prokineticins are a highly conserved small peptide family expressed in all vertebrates, which contain a broad spectrum of

functions. In this research, a prokineticin-like substance (Bv8-AJ) obtained from the poison of the frog *Amolopsjing dongensis* Bv8-AJ demonstrated a significant growth-promoting effect on both fibroblasts and keratinocytes taken from young mice by triggering the generation of interleukin (IL)-1 [43]. For drug development, the action of toxins must be studied to facilitate broad-spectrum analysis and develop taxon-specific effects on cancer cell lines [44]. These neglected animals contain bioactive molecules of therapeutic importance [45]. In recent times, natural toxins and their analogues are used as drug templates (Figure 2).

Anti-HIV activity

Specific frog skin peptides, such as caerin 1.1 and maculatin 1.1, exhibit potent anti-HIV activity by disrupting the virus and preventing its entry into host cells without harming the cells themselves [46]. These molecules can inhibit HIV from infecting T cells and can also block the transfer of HIV from dendritic cells to T cells. These peptides can disrupt the HIV envelope, a protective outer layer of the virus, and prevent the virus from attaching to and fusing with target cells. These peptides, from Australian tree frogs, inhibit HIV infection of T cells within minutes of exposure at non-toxic concentrations [47] (Figure 2).

Insecticidal activity

Frog skin secretions contain a variety of bioactive molecules with potent insecticidal and repellent activities. These compounds, including peptides and biogenic amines, can cause significant mortality and behavioural changes in various insects, particularly mosquitoes and blowflies. Biogenic amines, such as leptodactyline found in *Leptodactylus* species, have marked neuromuscular-blocking effects that lead to rapid paralysis and death in insects. The insecticidal activity of frog toxins primarily involves neuromuscular disruption and physical damage to cell membrane. The anuran skin secretions exhibit insecticidal activity, contact toxicity, and repellency against mosquitoes [48-50]. The present study aimed to investigate the insecticidal activity of crude skin secretions extracted from the frogs *Leptodactylus knudseni* and *Phyllomedusa vaillantii* on the main vectors of malaria and dengue fever in Brazil, *Anopheles darlingi* and *Aedes aegypti*, respectively [51]. Similarly, Volatiles from *Litoria rubella* and *Uperoleiamjo bergi* secretions were repellent to *C. annulirostris*in amphibians, which is novel and demonstrates that many aspects of frog chemical ecology remain unexplored [50] (Figure 2).

Natural toxins and synthetic analogues potentially constitute the basis of toxin weapons. These include, for example, cases of new toxins from natural sources, their chemical synthesis, and the development of toxin weapons [52]. Frogs possess diverse biochemicals/molecules whichare used in skin defence [1]. This is the evolutionary character of the frog, which has poison glands actively involved in chemical defence [11]. Diverse microbial assemblages inhabit amphibian skin and are known to differ among species.

Mode of action

It is clear that actual envenomation (active injection) in frogs is rare and involves specialised bony head spines, while typical poisonous frogs rely on passive defence through skin secretions. These possess bony spines on their skulls that are covered by a thin layer of skin containing highly toxic secretions. This is quite dissimilar to other venomous animals. Frogs use poison when threatened by a predator. The frogs flex their heads in an unusual vertical and lateral motion to jab the spines into the attacker's skin or mouth. Their defense is passive; they secrete toxins onto their skin from granular glands. A predator is harmed only if it bites, chews, or otherwise contacts the toxins through a mucous membrane or wound. Frog toxins act through exposure to predators' skin, and their specific mode of action depends on the chemical. Phyllobates poison dart frogs secrete batrachotoxin, which acts on sodium channels to cause paralysis and cardiac arrest, while others, like epibatidine, block acetylcholine receptors. Some frogs secrete peptide toxins (e.g., caerulein, bombesin, dermorphin) that act as potent ligands for various receptors (like cholecystokinin or opioid receptors) in a predator's body. These can induce nausea, hypotension, and muscle spasms.Frogs also secrete antimicrobial peptides (AMPs), which act as molecular toxin delivery systems. Pumiliotoxins (PTXs) primarily act as positive modulators of voltage-gated sodium channels (VGSCs), which causes a "lethal storm of hyperactivity" in nerve and muscle cells by disrupting the normal flow of ions. Few toxins directly enter the bloodstream, affect cell permeability, and target specific organs.

Toads of the Bufo genus secrete cardioactive steroids (like digoxin) that can cause irregular and life-threatening heart rhythms

and even cardiac arrest in predators. The overstimulation of nerve and muscle cells can cause them to fire continuously, preventing the transmission of proper signals. This leads to a loss of normal function, eventually resulting in paralysis. The toxin acts by hyperactivating the sodium channel that generates action potentials in nerves and muscle, thereby causing a lethal storm of hyperactivity in nerves, synapses, and muscle cells. Neuropeptides like batrachotoxin exert their effects on axonal and myelinated fibres. Frog venom toxins bind to nicotinic acetylcholine receptors (nAChRs), which are prototypical ligand-gated ion channels, provide cholinergic signalling, and are modulated by various venom toxins and drugs in addition to neurotransmitters.

Further, the level of toxicity of toxins depends on the ecology of the area, and the molecular physiology and immune defence of the animal. It is also true that toxins link the behaviour of prey and predators among animals. Cytotoxins from frogs easily target cancer cells and disturb their membrane integrity. These toxins heavily act upon various ion channels and pumps, which actively maintain the flow of ions across the membrane. The vitality of cells and tissues depends on respiration or oxygen consumption by the body cells. Frog toxins target the endomembrane system and cytochrome systems.

Conclusions

Frog secrete toxins which show diverse structural variability and biological activity.. These natural toxin molecules from different frog species are poisonous in nature. These show anti-inflammatory, anaesthetic, antidiabetic, anticancer, HIV, and insecticidal properties. These could be utilised as molecular and cellular biology tools to aid in diagnosing the disease. These possess wound healing properties and could be used to relieve from severe pain. These bound to various channels and inactivate their vitality, hence frog toxins could be used as anaesthetics and analgesic agents. There is also a need to understand the molecular mechanisms of toxin action, and behaviour in biological system. These natural toxin molecules could be used to create new drug templates for novel therapeutic targets.

Acknowledgments

The authors are thankful to HOD and Dean, Faculty of Science.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

Bibliography

1. Raaymakers C., *et al*. "A New Family of Diverse Skin Peptides from the Microhylid Frog Genus Phrynomantis". *Molecules* (2020): 912.

2. Corrêa BAAP., *et al*. "Report of envenomation in humans by handling a dyeing poison frog Dendrobates tinctorius (Schneider, 1799) (Anura: Dendrobatidae) in the Amazon". *Revista da Sociedade Brasileira de Medicina Tropical* 54 (2020): e04612020.

3. Lin Y., *et al*. "Ranatensin-HL: A Bombesin-Related Tridecapeptide from the Skin Secretion of the Broad-Folded Frog, *Hylarana latouchii*". *Molecules* 22.7 (2017): 1110.

4. Zhou X., *et al*. "Pharmacological Effects of Two Novel Bombesin-Like Peptides from the Skin Secretions of Chinese Piebald Odorous Frog (*Odorranasch mackeri*) and European Edible Frog (*Pelophylax kl. esculentus*) on Smooth Muscle". *Molecules* 22.10 (2017): 1798.

5. Rádis-Baptista G., *et al*. "Cell-Penetrating Peptides Derived from Animal Venoms and Toxins". *Toxins (Basel)* 13.2 (2021): 147.

6. Vallejo JR., *et al*. "Histological Study of Glandular Variability in the Skin of the Natterjack Toad-*Epidalea calamita* (Laurenti, 1768)-Used in Spanish Historical Ethnoveterinary Medicine and Ethnomedicine". *Veterinary Sciences* 9.8 (2022): 423.

7. Mo GX., *et al*. "A Novel Insulinotropic Peptide from the Skin Secretions of *Amolops loloensis* Frog". *Natural Products and Bioprospecting* 4.5 (2014): 309-313.

8. ShiD., *et al*. "Baltikinin: A New Myotropic Tryptophyllin-3 Peptide Isolated from the Skin Secretion of the Purple-Sided Leaf Frog, *Phyllomedusa baltea". Toxins (Basel)* 8.7 (2016): 213.

9. Fusco LS., *et al*. "Biochemical characterization and cytotoxic effect of the skin secretion from the red-spotted Argentina frog *Argenteo hylasiemersi* (Anura: Hylidae)". *Journal of Venomous Animals and Toxins* 26 (2020): e20190078

10. Jeckel AM ., *et al*. "The relationship between poison frog chemical defenses and age, body size, and sex". *Frontiers in Zoology* 12 (2015): 27.

11. Jared C, *et al*. "Skin gland concentrations adapted to different evolutionary pressures in the head and posterior regions of the caecilian *Siphonops annulatus". Scientific Report* 8.1 (2018): 3576.

12. Rodriguez C., *et al*. "Antimicrobial Secretions of Toads (Anura, Bufonidae): Bioactive Extracts and Isolated Compounds against Human Pathogens". *Antibiotics (Basel)* 9.12 (2020): 843.

13. Gong Y., *et al*. "Structural and bio-functional assessment of the postaxillary gland in *Nidirana pleuraden* (Amphibia: Anura: Ranidae)". *Zoological Letter* 6 (2020): 7.

14. Antoniazzi MM., *et al*. "Reproductive behaviour, cutaneous morphology, and skin secretion analysis in the anuran *Dermatonotus muelleri"*. *iScience* 25.4 (2022): 104073.

15. Gowda RM., *et al*. "Toad venom poisoning: resemblance to digoxin toxicity and therapeutic implications". *Heart* 89.4 (2003): e14.

16. Bordon KCF., *et al*. "From Animal Poisons and Venoms to Medicines: Achievements, Challenges and Perspectives in Drug Discovery". *Frontiers in Pharmacology* 11 (2020): 1132.

17. Zou D., *et al*. "Bufadienolides originated from toad source and their anti-inflammatory activity". *Frontiers in Pharmacology* 13 (2022): 1044027.

18. Chen N., et al. "The advancement of structure, bioactivity, mechanism, and synthesis of bufotalin". Steroids 214 (2025): 109555.

19. Daly JW., *et al*. "Histrionicotoxins: roentgen-ray analysis of the novel allenic and acetylenie spiroalkaloids isolated from a Colombian frog, *Dendrobates histrionicus*". (1971).

20. Khodorov BI., *et al*. "Batrachotoxin as a tool to study voltage-sensitive sodium channels of excitable membranes". *Progress in Biophysics & Molecular* Biology 45.2 (1985): 57-148.

21. Wang SY., *et al*. "Single rat muscle Na+ channel mutation confers batrachotoxin autoresistance found in poison-dart frog *Phyllobates terribilis*". *Proceedings of the National Academy of Sciences* 114.39 (2017): 10491-10496.

22. Myers., *et al*. "Dart-Poison Frogs". *Scientific American* (1983): 120-133.

23. Patocka., *et al*. "Dart Poison Frogs and their Toxins". *The ASA (Applied Science and Analysis) Newsletter* (2000): 99-95.

24. Schofield GG., *et al*. "The effect of pumiliotoxin-B on the excitability of bullfrog sympathetic neurons". *European Journal of Pharmacology* 147.1 (1988): 39-48.

25. Chen K. K.,*et al*. ."Pharmacology and toxicology of toad venom". *Journal of Pharmaceutical Sciences* 56 (1967): 1535-1541.

26. Zohrab F., *et al.* "Biological Properties, Current Applications and Potential Therapeutic Applications of Brevinin Peptide Superfamily". *International Journal of Peptide Research and Therapeutics* 25.1 (2019): 39-48. .

27. Xi X., *et al*. "A review on bradykinin-related peptides isolated from amphibian skin secretion". *Toxins (Basel)* 7.3 (2015): 951-70.

28. Brunetti AE., *et al*. "Odorous secretions in anurans: morphological and functional assessment of serous glands as a source of volatile compounds in the skin of the treefrog *Hypsiboas pulchellus* (Amphibia: Anura: Hylidae)". *Journal of Anatomy* 228.3 (2016): 430-442.

29. Anastasi A., *et al*. "Isolation and structure of bombesin and alytesin, two analogous active peptides from the skin of the European amphibians *Bombina and alytes*". *Experientia* 27 (1971): 166-167.

30. RončevićT., *et al*. "Parallel identification of novel antimicrobial peptide sequences from multiple anuran species by targeted DNA sequencing". *BMC Genomics* 19.1 (2018): 827

31. Ong D., *et al*. "Protein Composition and Biomedical Potential of the Skin Secretion of *Hylaranaery thraea* (Schlegel, 1837) (Anura: Ranidae) from Langkawi Archipelago, Kedah, Peninsular Malaysia". *International Journal of Peptide Research and Therapeutics* 27.3 (2021): 2125-2133.

32. Jeong MC., *et al*. "Investigation of cationicity and structure of pseudin-2 analogues for enhanced bacterial selectivity and anti-inflammatory activity". *Scientific Report* 7.1 (2017): 1455.

33. Amatya R., *et al*. "Drug Delivery Strategies for Enhancing the Therapeutic Efficacy of Toxin-Derived Anti-Diabetic Peptides". *Toxins (Basel)* 12.5 (2020): 313.

34. Cruz e Carvalho A., *et al*. "Cytotoxic Activity and Antiproliferative Effects of Crude Skin Secretion from *Physalaemus nattereri* (Anura: Leptodactylidae) on in vitro Melanoma Cells". *Toxins (Basel)* 7.10 (2015): 3989-4005.

35. Chen Q., *et al*. "Amphibian-Derived Natural Anticancer Peptides and Proteins: Mechanism of Action, Application Strategies, and Prospects". *International Journal of Molecular Sciences* 24.18 (2023): 13985.

36. Bókony V., *et al*. "Toads phenotypically adjust their chemical defences to anthropogenic habitat change". *Scientific Report* 9.1 (2019): 3163.

37. Pabijan M., *et al*. "Evolutionary principles guiding amphibian conservation". *Evolutionary Applications* 13.5 (2020): 857-878.

38. Crossland MR., *et al*. "Chemical cues that attract cannibalistic cane toad (*Rhinella marina*) larvae to vulnerable embryos". *Scientific Report* 11.1 (2021): 12527.

39. Douglas TE, *et al*. "Trade-offs between cost of ingestion and rate of intake drive defensive toxin use". *Biological Letter* 18.2 (2022): 20210579.

40. Hossie TJ., *et al*. "Increasing availability of palatable prey induces predator-dependence and increases predation on unpalatable prey". *Scientific Report* 11 (2021): 6763.

41. Wei S., *et al*. "Characteristics of hemolytic activity induced by skin secretions of the frog K*aloula pulchra hainana". Journal of Venomous Animals and Toxins* 19.1 (2013): 9.

42. Armstrong CE., *et al*. "Electrical properties of frog saccular hair cells: distortion by enzymatic dissociation". *Journal of Neuroscience* 18.8 (1998): 2962-2973.

43. Chang J., *et al*. "Bv8-Like Toxin from the Frog Venom of *Amolops jingdongensis* Promotes Wound Healing via the Interleukin-1 Signaling Pathway". *Toxins (Basel)* 12.1 (2017): 15.

44. Han Liu *et al*, "A potential wound healing-promoting peptide from frog skin". *The International Journal of Biochemistry & Cell Biology* 49 (2014): 32-41.

45. Coelho GR., *et al*. "Neglected Venomous Animals and Toxins: Underrated Biotechnological Tools in Drug Development". *Toxins (Basel)* 13.12 (2021): 851.

46. Ni G., *et al*. "Comparative proteomic study of the antiproliferative activity of frog host-defence peptide Caerin 1.9 and its additive effect with Caerin 1.1 on TC-1 cells transformed with HPV16 E6 and E7". *Biomed Research International* (2018).

47. Ni G., *et al*. "Host-defense peptides Caerin 1.1 and 1.9 stimulate TNF-alpha-dependent apoptotic signals in human cervical cancer HeLa cells". *Frontiers in Cell and Developmental Biology* 8 (2020): 676.

48. Weldon PJ., *et al*. "A common pumiliotoxin from poison frogs exhibits enantioselective toxicity against mosquitoes". *Proceedings of the National Academy of Sciences* 103.47 (2006): 17818-17821.

49. Williams CR., *et al*. "Toxicity of green tree frog (Litoria caerulea) skin secretion to the blowflies *Calliphora stygia* (Fabricius) and *Lucilia cuprin*a (Wiedemann) (Diptera: Calliphoridae)". *Austral Entomology* 37.1 (1998): 85-89.

50. Williams CR., *et al*. "Mosquito repellents in frog skin". *Biological Letter* 2.2 (2006): 242-245.

51. Trindade FT., *et al*. "Insecticidal activity of *Leptodactylus knudseni* and *Phyllomedusa vaillantii* crude skin secretions against the mosquitoes Anopheles darlingi and Aedes aegypti". *Journal of Venomous Animals and Toxins* 20 (2014): 28.

52. Pitschmann V., *et al*. "Military Importance of Natural Toxins and Their Analogs". *Molecules* 21.5 (2016): 556.

53. Vandendriessche T., *et al*. "Modulation of voltage-gated Na+ and K+ channels by pumiliotoxin 251D: a "joint venture" alkaloid from arthropods and amphibians". *Toxicon* 51.3 (2008): 334-344.

54. Yin P H., *et al*. "Anti-tumor activity and apoptosis-regulation mechanisms of bufalin in various cancers: New hope for cancer patients". *Asian Pacific Journal of Cancer Prevention* (2012): 5339-5343.

55. Yang EH., *et al*. "Digitalis toxicity: a fading but crucial complication to recognize". *American Journal of Medicine* 125 (2012): 337-343.

56. Cui X., et al. "Anti-hepatitis B virus activities of cinobufacini and its active components bufalin and cinobufagin in HepG2.2.15 cells". Biological and Pharmaceutical Bulletin 33.10 (2010): 1728-1732.

57. Xie JT., et al. "Cardiac toxicity of resibufogenin: electrophysiological evidence". Acta Pharmacologica Sinica 22.4 (2009): 289-297.

58. Costa TO., et al. "Occurrence of bufotenin in the Osteocephalus genus (Anura: Hylidae)". Toxicon 46.4 (2005): 371-375.

59. El-Seedi HR., et al. "Chemistry and the Potential Antiviral, Anticancer, and Anti-Inflammatory Activities of Cardiotonic Steroids Derived from Toads". Molecules 27.19 (2022): 6586

60. Zhao L., et al. "Toxicokinetics of Arenobufagin and its Cardiotoxicity Mechanism Exploration Based on Lipidomics and Proteomics Approaches in Rats". Frontiers in Pharmacology 12 (2021): 780016.