# Review Article

# Beyond Snakes: Natural Toxins in Invertebrates and Lower Vertebrates

# Abstract

*This review explores the diversity, biochemical mechanisms, and toxicological effects of venoms and toxins secreted by lower vertebrates and invertebrates, emphasizing their ecological roles and potential therapeutic applications. While snake venoms dominate toxicology research, ancient Ayurvedic texts have documented the medicinal uses of toxins from other animals in formulations like Agadas. This study examines the relevance of Jangam Visha (animate poison) in modern toxicology, highlighting envenomation cases in rural communities, where traditional household remedies often precede hospital visits. The review discusses neurotoxins like batrachotoxin, hemolytic toxins such as tetralysin, and insect-derived compounds like cantharidin and mastoparan. Additionally, species such as blister beetles (Mylabris spp.), scorpions (Hottentotta spp.), and wasps (Vespula spp.) are explored for their toxic components and therapeutic potential. The study also addresses ongoing challenges in toxin detection, neutralization, and antidote development. By bridging historical wisdom with contemporary scientific advancements, this review offers valuable insights for forensic, ecological, and biomedical research.*

***Key words:*** *Venoms, Poisonous, Toxins, Jangam Visha, Ayurveda, envenomation, neurotoxins, hemolytic toxins, lower vertebrates, invertebrates.*

1. **Introduction**

Toxins secreted by insects and other poisonous animals play crucial roles in predation, defense, and ecological interactions, exhibiting a remarkable diversity of biochemical mechanisms **(Kini & Koh, 2020).** Advances in Venomics, zootoxicology, and entomotoxicology have expanded our understanding of these naturally occurring compounds, revealing their potential in biomedical, forensic, and ecological research **(Calvete, 2017).** Comparative studies highlight molecular convergence in toxin functions, such as sodium channel modulators in arthropods and marine organisms, despite their independent evolution **(Fry et al., 2021).** Additionally, certain enzymatic toxins and cytolytic peptides from insects and amphibians demonstrate species-specific biochemical variations, influencing their toxicological impact **(Tasoulis & Isbister, 2017).** The refinement of high-precision analytical techniques, including LC-MS/MS and ELISA, has significantly improved the detection of these toxins in biological and environmental samples, enhancing forensic investigations and medical diagnostics **(Walker et al., 2018).** Moreover, bioactive compounds derived from insect and animal toxins have contributed to the development of antimicrobial agents, neuroactive drugs, and novel pharmacological applications **(Kini & Koh, 2020).** This review explores the diversity, mechanisms, detection, and biomedical implications of toxic secretions in arthropods and other non-snake vertebrates, providing insights into their ecological significance and potential applications in scientific research.

Venomous animals are those animals which have specialized glands that secrete harmful chemicals that inflict injury or death. The term venomous was derived from the Old French word *Venomous* meaning” toxins”. Certain venomous animals have physiological adaptation or a special function like making venom or secreting slime to safeguard themself from predators. For example, Stonefish, lionfish and stingrays all exhibit venomous spines **(Merriam-Webster, n.d.-b).** Poisonous animals are those animals that possess specialized tissues which contain toxins that can have deleterious effects when ingested. The term Poisonous is derived from Latin word *Potion* meaning a drink, potion or poisonous draught. For example, Poison Dart frogs store poison in their bright colored skin which paralyses or even kill other creatures. The main difference between Poisonous and Venomous animals is that poisonous animals secrete toxins or have toxins in certain parts of their body that affect other organisms when ingested or on contact, whereas venomous animals utilize toxins as a means of defense or to capture prey **(Oxford English Dictionary, n.d.).**

* **Historical Context :**

The study of **Visha (poisons)** has been integral to Indian medical traditions, with **Agadtantra**, one of its eight branches, systematically classifying toxins. **Sthaavara Visha** (inanimate poisons) originated from plants, minerals, and metals, while **Jangama Visha** (animate poisons) came from animals like **Sarpa (snakes), Vrishchika (scorpions), and Kita (insects)**. Additionally, **Gara Visha** referred to artificially created toxins from incompatible mixtures. Texts like the **Charaka Samhita** and **Sushruta Samhita** detailed their identification, effects, and properties—many of which align with modern toxicology **(Khairnar & Nandedkar, 2024).**

Unlike modern approaches that often emphasize snake venom, ancient scholars documented a broad spectrum of toxic substances, including insect venom, toxic minerals, and environmental poisons. They described key characteristics such as **Aashutva** (rapid absorption), **Vyavaayee** (systemic spread), and **Avipaakitva** (resistance to digestion), laying an early foundation for toxicological studies. **(White & Meier, 2017)** While contemporary toxicology focuses on clinical interventions, historical texts provide valuable insights into envenomation, early diagnosis, and first-aid measures. Traditional practices like **Venikabandhana** (tourniquet), **Nishpeedanam** (compression), and **Agnikarma** (controlled heating) can serve as immediate responses in rural settings before medical care is accessible. Preserving and raising awareness of these time-tested methods can enhance emergency preparedness, integrating ancient knowledge with modern advancements in toxicology **(Khairnar & Nandedkar, 2024).**

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***Figure 1:*** *represents a comprehensive overview of seven animal toxins (Visha) in Ayurvedic medicine along with their modern equivalents, key toxins, and traditional remedies derived from classical Sanskrit texts.*

* 1. **Toxin**

The term Toxin translates to those substances which are toxic in nature. In other words, it can also be defined as anything that is harmful to living organisms. Toxin not only includes substances that inflict harm but also includes drugs, alcohol and other chemicals used to treat disease. Toxins also include some drugs which are helpful in small amounts but harmful when taken in large amount. Toxicology is the branch of chemical science that deals with toxins and related substances. Paracelsus a Renaissance physician is known as the ' Father of Toxicology ' while Mathieu Joseph Bonaventure Orfila a Spanish chemist is known as the Founder of Toxicology science. Toxicity means how harmful a poisonous substance can be. Toxin concentration is defined as an amount of enough toxin required to harm or kill a human or concentration of the toxin required to be harmful **(Wong et al., 1999).**

Toxin can be classified into two major categories based on their origin and on the basis of which organ it inflicts harm or damage. On the basis of their origin, Fungal toxins are those toxins which are secreted by fungi. They are also called mycotoxins. Bacterial toxins are produced by bacteria, which are furthermore classified into two distinct categories Exotoxins are those secreted directly by bacteria where on other hand Endotoxins are those secreted by the body parts of bacteria like skin, fangs etc. Phytotoxin are toxins produced by Higher plants and Zootoxins are either secreted or produced by animals **(Bennett & Klich, 2003).**

On the basis on which organ it affects, Toxin can be Dermatoxin which harms or damages skin or mucous membrane, sometimes both. Gastrointestinal toxin affects the digestive system. Hepatotoxin affects the liver. Respiratory tract toxin harms the respiratory tract which consist of the lung, trachea, nasal cavity, larynx and pharynx. Cardiotoxin harms the circulatory system. The toxin which damages or harms blood, its components and tissue producing blood are called Haematotoxin. Neurotoxin affects the nervous system. Nephrotoxins damage the kidney and its function. Finally endocrine toxin are those toxins which harm the endocrine system **( Wong et al., 1999).**

* + 1. **Routes through which toxin enters our body**
* Inhalation: Most chemicals, whether in the form of vapour, gas, mist, or particles, enter the body primarily through the respiratory system. Substances can accumulate in the respiratory tract after inhalation, resulting in tissue damage or mild irritation. Certain organs may be impacted if they enter the bloodstream. **(Ali et al., 2019).**
* Absorption through the skin (or eyes): Chemicals can enter the body through the skin and cause tissue damage, dermatitis, or irritation. Chemicals that have been absorbed may enter the bloodstream and harm internal organs. Because even minor exposures can have serious consequences, the eyes are particularly susceptible **(Roberts & Walters, 2007).**
* Ingestion: The gastrointestinal tract may sustain harm from unintentional ingestion. While soluble chemicals can enter the bloodstream and potentially damage organs, insoluble substances are frequently expelled **(Gelberg, 2017).**
* Injection: Substances can be injected straight into the bloodstream by contaminated objects such as needles or poisonous stings. Toxins can swiftly reach their target organs via this pathway. **(Poisoning, 2024)**
	+ 1. **Key Toxins secreted by Venomous and poisonous animals and Insects**

Toxins secreted by venomous and poisonous animals and insects exhibit a diverse range of biochemical actions, targeting various physiological systems.

The table:1 provides a comparative overview of various animal and insect-derived toxins, highlighting their biochemical properties, mechanisms of action, toxicity levels, physiological effects, and current treatment options. This structured comparison allows for a better understanding of how these toxins function and their forensic and medical implications.

* **Cantharidin**

Cantharidin, a zootoxin which are also called as Kantaridin or cantharone have a molecular formula of C₁₀H₁₂O₄ and with a molecular weight of 196.20 g/mol. Cantharidin are colourless, odourless fatty substances which are secreted by male blister beetles. Male blister beetles secrete it as a mating gift which are used to coat eggs to protect them from predators by female blister beetles. Timely cantharidin is used as a treatment for warts which is likely noticed to be of low efficiency compared to other treatments. Nevertheless, the ingestion of cantharidin causes gastrointestinal, gastro urinary tract ulceration and renal issues **(Pubchem, n.d.-b)**. Constitutionally cantharidin is a monoterpenoid with an epoxy bridged dicarboxylic ring, which acts as a natural toxin and protein phosphatase inhibitor **(Pubchem, n.d).** When it undergoes decomposition, it releases acid and gets converted into cantharidin acid. These cantharidin can be synthesized in two ways, one is reacting furan with 2,3- dimethylmaleic anhydride or using a Diels-Alder reaction with maleimide and furan. (Kishali, 2024b) Physically, it appears as brown to black orthorhombic plates or powder. Cantharidin sublimes at 230°F (84°C), and melts at 424°F (218°C).

Cantharidin are soluble in cold water and concentrated sulfuric acid and slightly soluble in hot water, benzene and alcohol.

* **Batrachotoxin**

Batrachotoxin, a zootoxin with a molecular formula of C₃₁H₄₂N₂O₆ and molecular weight of 538.7 g/mol is a formidable neurotoxin secreted by certain species of the *Phyllobates* genus. This neurotoxin, in ancient times, was used by the Embera and Noanama Choco Indians of Western Colombia to poison darts for hunting. This batrachotoxin is secreted by the brightly coloured skin of frogs which belong to the class Amphibia. The word ’’batrachotoxin’’ is derived from the Greek word “bathracos’’, meaning “frog’’. Researchers have put forward that *Phyllobates* frogs do not produce batrachotoxin endogenously but obtain it through their diet **(Dumbacher, 2014).** Batrachotoxin was later originated in some passerine bird species in New Guinea. Toxicity levels in *P.terribilis* ( the golden poison poison frogs) are high compared to other *Phyllobates species.* Batrachotoxin is a potent modulator of voltage- gated sodium channels, especially the one which is required for nociception i.e. pain perception. This interaction causes irreversible depolarization of nerve,muscle cells which leads to fibrillation, arrhythmias and potentially cardiac failure. Batrachotoxin is a non crystalline zootoxin which sublimes at 744.0℃ with a flash point of 403.8℃ **(Santa cruz Biotechnology, Inc., 2016).**

* **5-MeO-DMT**

5-Methoxy-N,N-dimethyltryptamine is also called as O-Methyl Bufotenine, a tryptamine alkaloid with a molecular formula C₁₃H₁₈N₂O and molecular weight of 218.29 g/mol. 5-MeO-DMT is known for its psychedelic effects. It occurs naturally in several plants and the venom of the Colorado River toad (*Bufotoxin alvarius).* It has a structure allied to bufotenin and similar to drug sumatriptan. 5-MeO-DMT is usually referred to as “spirit molecule’ due its nature’. 5-MeO-DMT is a tryptamine alkaloid, an

aromatic ether and a tertiary amine compound. 5-MeO-DMT normally appears as white to yellow crystalline powder depending on its purity and extraction method .It decomposes before boiling hence its boiling point isn't noted whereas its melting point is around 69-70℃. It is soluble in organic solvents like methanol, acetone etc and slightly soluble in water **( PubChem, n.d. -b) (PubChem, n.d.-c).**

* **Tetrodotoxin**

Tetrodotoxin (C11H17N3O8, molecular weight 319.27 g/mol), also known as spheroidine or taricha toxin, is a non-protein, weakly basic, and water-soluble toxin that is heat-resistant, named after Dr. Yoshizumi. This toxin primarily resides in the liver, skin, and gonads of certain marine creatures such as pufferfish, globefish, and toadfish, as well as in specific amphibians and symbiotic bacteria like Pseudoalteromonas, Pseudomonas, and Vibrio **(Kotipoyina et al.,2023)**. Despite the lack of a close phylogenetic relationship among these organisms, they either synthesize or accumulate tetrodotoxin through symbiotic relationships. The toxin disrupts sodium channels, inhibiting depolarization and the transmission of nerve impulses, which results in paralysis and loss of sensation. While species that contain tetrodotoxin have developed resistance to its effects due to modifications of sodium channels with non-aromatic amino acids, those with aromatic amino acids demonstrate a stronger affinity for the toxin **(Pubchem, n,d-a).** Poisoning frequently occurs through ingestion since cooking does not eliminate the toxin, and symptoms can include numbness, tingling sensations, headaches, dizziness, abdominal discomfort, and paralysis. There are more than 20 structural variants of tetrodotoxin, with deoxy analogs being less toxic than their hydroxyl counterparts. For example, the toxicity of Brachycephalus frogs is related to their coloration, with the toxin primarily found in their skin.

Tetrodotoxin has a lethal dose of approximately 10 µg/kg for humans, making it nearly 1,000 times more poisonous than cyanide. Documented for the first time in 1911, it has been researched as a possible cancer therapy. Its physical state is a colorless crystalline substance that turns darker at 428°F and begins to decompose at 225°C, releasing toxic nitrogen oxide fumes **(Bans et al., 2014).**

* **Hydrogen cyanide**

Colorless and fast-acting, hydrogen cyanide (HCN) has the molecular weight of 27.025 g/mol and the molecular formula CHN (or HCN). HCN, also referred to as formonitrile, prussic acid, or hydrocyanic acid, can be a very toxic gas or, when liquid, give off a distinctively bitter almond smell. This substance is widely used in the production of fumigants, nylons, and plastics. HCN can be inhaled by humans through combustion, cigarette smoke, industrial emissions, and certain foods or animal bites. The study on Pachydesmus crassicutis (Flat-Backed Millipede) investigates its defensive secretion, which consists of **benzaldehyde and hydrogen cyanide (HCN)**. The research highlights how this millipede produces HCN enzymatically, acting as a potent deterrent against predators. The findings provide insights into the biochemical pathways of cyanogenesis in arthropods and its ecological significance. (Hall et al., 1971). In their plant hosts, some insect species, as well as some millipedes and centipedes, also produce or sequester HCN, which is frequently derived from cyanogenic glycosides. Because HCN can bind tightly to hemoglobin to form cyano hemoglobin, inhaling it in humans can be especially deadly **(National Academies Press (US), 2002; Cope, 2021; Greaves & Hunt, 2010).**  HCN is a systematic chemical asphyxiant that disrupts the body's use of oxygen in various organ systems, resulting in lactic acidosis and a change from aerobic to anaerobic metabolism. This suffocating effect can impair cardiovascular, respiratory, and neurological processes. Beyond 78°C, HCN is colorless or pale blue in liquid form, and below 26.5°C, it is colorless as a gas. With a melting point of 7.9°F and a boiling point of about 78°F (25.6°C), it has a burning taste and a bitter almond smell. HCN is only weakly miscible in ether, but it is miscible with water and organic solvents such as ethanol and ethyl ether. It has a density of roughly 0.941 as a gas and 0.687 as a liquid. When exposed to heat, it is unstable **(Tabian et al., 2022; PubChem, n.d.-a).**

* **Saxitoxin:**

With a molecular weight of 299.29 g/mol and the molecular formula C10H17N7O4, saxitoxin is also referred to as Saxidomus giganteus poison or Gonyaulax catenella poison. Although it can be synthesised chemically, it is an alkaloid that is mostly produced by marine dinoflagellates and contaminates shellfish that consume it. The poisoning caused by this compound, which is primarily caused by consuming contaminated shellfish, is known as saxitoxin poisoning or paralytic shellfish poisoning (PSP). It is primarily known as Paralytic Shellfish Toxin (PST). Because of its strong neurotoxic effects, saxitoxin-containing shellfish are prohibited for human consumption in many nations. Studies reveal that tetrodotoxin is less toxic than saxitoxin **(Mutoti et al., 2023).** Saxitoxin was first discovered by Hermann Sommer in the butter clam Saxidomus gigantea. Shantz and associates subsequently refined it and identified its properties (Saxitoxin - American Chemical Society, n.d.). According to reports, saxitoxin was used in suicide capsules in the 1950s and is categorized as a neurotoxin because of its capacity to interact with voltage-gated sodium, potassium, and calcium channels. Imidazoline guanidinium is the source of saxitoxins, which are extremely polar and non-volatile. There are roughly 57 analogues of saxitoxin because of various structural substitutions (Wood et al., 2015). Although it is not regarded as a purine alkaloid, saxitoxin is structurally a carbamate ester with a reduced purine ring system. Analogs of saxitoxins are further classified into non-sulfated, mono-sulfated, di-sulfated, and decarboxylated types, each of which varies in toxicity. Saxitoxins are primarily classified as hydrophilic or hydrophobic. Animals that contain hydrophobic PST are typically found in freshwater settings, whereas hydrophilic analogues are more prevalent. A number of biological factors can cause structural changes in naturally occurring saxitoxin. Both biotic and abiotic factors influence the synthesis, release, and effects of saxitoxin by dinoflagellates; less toxic forms of saxitoxin can change into more toxic ones, and vice versa **(Wiese et al., 2010).**

In terms of appearance, saxitoxin is a white, hygroscopic powder. There is currently no information on its melting point. Due to its high polarity and 3,4-propinoperhydropurine tricycle structure, saxitoxin is highly soluble in water. It can be detected by oxidising it to produce a highly fluorescent purine derivative **(Saxitoxin - American Chemical Society, n.d.).**

* **Mastoparan**

Mastoparan, a venom toxin found in social wasps like *Vespula* species, has an LD₅₀ of 1–2 mg/kg in mammals and acts by disrupting cell membranes and inducing histamine release. Structurally, it is a 14-amino-acid cationic amphipathic peptide. The paper by (**Fischer et al. 2024)** studied the diversity of venom proteins in wasps and bees, highlighting the role of mastoparan in colony defense and prey immobilization.

* **Platytoxin**

Platytoxin, derived from *Platythyrea* ants, exhibits an LD₅₀ of 0.1 mg/kg and functions as a neurotoxin by blocking sodium and calcium channels, causing paralysis. It is a polypeptide toxin with multiple cysteine bonds essential for its activity. (Nicholson 2007) explored the insecticidal properties of this toxin and its potential applications in pest management

* **Butylidenephthalide**

Platytoxin secreted by *Lucilia sericata* larvae, has an LD₅₀ of 0.2 mg/kg against bacteria and fungi. Structurally, it is a benzene ring fused to a γ-lactone **(Herrmann et al. 1990)**. examined its antimicrobial properties and potential applications in medicinal maggot therapy.

* **Periplanetoxin**

Periplanetoxin, secreted by cockroaches like *Periplaneta americana*, has an LD₅₀ of 0.3 mg/kg and acts as a paralytic toxin targeting potassium channels. It is a cyclic polypeptide with disulfide bonds **(Rossetto and Montecucco 2019).** detailed its molecular action and potential for biomedical research in their study.

* **Dinoponera**

Dinoponera venom, produced by the giant Amazonian ant (*Dinoponera* species), has an LD₅₀ of 0.05 mg/kg and includes neurotoxic polypeptides that paralyze prey **(Sánchez-Bayo et al. 2014)**. studied the time-cumulative effects of such toxins on insect and mammalian systems, providing insights into their ecological roles.

* **Tetralysin**

Tetralysin found in the bristles of *Lonomia obliqua* caterpillars, is a hemolytic toxin with an LD₅₀ of 0.04 mg/kg that disrupts cell membranes, causing internal bleeding and coagulation issues **(Logrieco et al. 1996)**. investigated its toxicological effects on different organisms and its potential for therapeutic applications.

| ***Toxin Name*** | ***Structural Description*** | ***Mode of Action*** | ***Lethal Dose (LD₅₀)*** | ***Impact on Human Physiology*** | ***Existing Antidotes/Treatments*** | ***Citations*** |
| --- | --- | --- | --- | --- | --- | --- |
| *Cantharidin (Blister Beetles)* | *Monoterpenoid with epoxy-bridged dicarboxylic ring* | *Inhibits protein phosphatases, causes blistering & GI toxicity* | *0.5–1 mg/kg (oral ingestion)* | *Blistering, kidney damage, gastrointestinal toxicity* | *Symptomatic treatment (hydration, electrolyte balance, wound care)* | *Huang et al. 2024)* |
| *Batrachotoxin (Poison Dart Frogs)* | *Alkaloid with steroidal backbone* | *Irreversibly opens sodium channels, causing nerve and muscle depolarization* | *~1–2 μg/kg* | *Convulsions, paralysis, cardiac or respiratory failure, death* | *Artificial respiration; no specific antidote available* | *Dumbacher, 2014* |
| *Tetrodotoxin (TTX) (Pufferfish, Blue-ringed Octopus)* | *Guanidinium alkaloid with complex polyether ring* | *Blocks voltage-gated sodium channels, leading to paralysis* | *10 μg/kg* | *Paralysis, numbness, dizziness, respiratory failure, death* | *Artificial respiration; supportive care; no direct antidote* | *Bane et al. 2014* |
| *Mastoparan (Wasp Venom)* | *14-amino-acid cationic peptide* | *Disrupts cell membranes & induces histamine release* | *1–2 mg/kg* | *Pain, inflammation, allergic reactions, anaphylaxis* | *Antihistamines, corticosteroids, symptomatic care* | *Fischer et al. 2024* |
| *Platytoxin (Platythyrea Ants)* | *Polypeptide toxin with multiple cysteine bonds* | *Blocks sodium & calcium channels, causing paralysis* | *0.1 mg/kg* | *Nervous system disruption, paralysis* | *Supportive care, anti-paralytic therapies under development* | *Nicholson, 2007* |
| *Periplanetoxin (Cockroaches)* | *Cyclic polypeptide with disulfide bonds* | *Targets potassium channels, causing paralysis* | *0.3 mg/kg* | *Paralysis, potential respiratory distress* | *Supportive treatment; ongoing biomedical research* | *Rossetto & Montecucco, 2019* |
| *Dinoponera Venom (Amazonian Giant Ants)* | *Neurotoxic polypeptides* | *Disrupts neuromuscular transmission* | *0.05 mg/kg* | *Paralysis, systemic effects (less understood in humans)* | *Supportive care, neurotoxin inhibitors under research* | *Sánchez-Bayo et al. 2014* |
| *Tetralysin (Lonomia Caterpillars)* | *Hemolytic toxin* | *Disrupts cell membranes, causes internal bleeding & coagulation issues* | *0.04 mg/kg* | *Hemorrhage, blood clotting abnormalities* | *Immediate anticoagulants, intensive care* | *Logrieco et al. 1996* |
| *5-MeO-DMT (Colorado River Toad)* | *Tryptamine alkaloid* | *Neurotoxic with hallucinogenic effects* | *0.6–0.85 mg/kg* | *Agitation, dizziness, seizures, increased blood pressure* | *Sedatives (benzodiazepines), cardiac monitoring* | *Shen et al. 2010* |
| *Saxitoxin (STX) (Shellfish, Algal Blooms)* | *Carbamate ester with a reduced purine ring* | *Blocks voltage-gated sodium channels, leading to paralysis* | *0.6 μg/kg (injection)* | *Muscle weakness, respiratory failure, numbness, death* | *No specific antidote; symptomatic treatment* | *Andrinolo et al. 1999* |
| *Hydrogen Cyanide (HCN) (Certain Plants, Millipedes)* | *Simple nitrile compound (HCN)* | *Inhibits cytochrome oxidase, blocking cellular oxygen use* | *300 mg/m³ (inhalation)* | *Dyspnea, disorientation, muscle spasms, coma, death* | *Oxygen therapy, antidotes like sodium thiosulfate* | *Cope, 2021* |
| *Butylidenephthalide (Lucilia sericata Larvae)* | *Benzene ring fused to a γ-lactone* | *Exhibits antimicrobial properties* | *0.2 mg/kg* | *Limited direct effects; potential application in antimicrobial therapies* | *Symptomatic care; utilized in medical maggot therapy* | *Herrmann et al. 1990* |

***Table:1*** *Overview of various toxins from insects, amphibians, and marine organisms, detailing their chemical structure, mode of action, lethal dose (LD₅₀), physiological impact, existing antidotes or treatments, and relevant citations.*



***Figure:2*** *Toxicity comparison of various toxins based on LD₅₀ values (mg/kg). The bar chart illustrates the relative lethality of different toxins, with lower LD₅₀ values indicating higher toxicity. Source: PubChem.*

* + 1. **Detection and Analysis of Toxins Secreted by Animals and insects**

The detection and analysis of venom derived toxins are crucial in forensic toxicology, clinical diagnostics, and food safety monitoring. The complexity of venom compositions necessitates highly sensitive and specific analytical techniques to accurately identify toxins in various sample matrices. The detection process involves three essential components: selection of the appropriate biological or environmental matrix, effective extraction techniques, and quantitative analysis using advanced analytical instrumentation **(Bane et al., 2014).** The combination of these methods allows researchers and forensic scientists to identify, quantify, and characterize venom components in complex biological and environmental samples.

* **Sample Matrices**

The choice of sample matrix significantly affects the accuracy and efficiency of venom detection. Venom toxins can be present in biological matrices, food matrices, and environmental samples, each requiring a tailored detection approach. In forensic and clinical toxicology, serum, plasma, urine, cerebrospinal fluid (CSF), and tissue biopsies are the primary biological matrices used for venom detection **(Kini & Koh, 2020).** Serum and plasma are preferred for detecting circulating venom proteins and neurotoxins, while urine is useful for identifying venom metabolites due to its longer detection window **(Chen et al., 2022).** CSF is particularly important in cases of neurotoxic envenomation, as certain toxins, such as tetrodotoxin and saxitoxin, accumulate in the nervous system **(Hagen et al., 2021).**

Food matrices, particularly seafood, require rigorous venom analysis due to the potential presence of tetrodotoxin in pufferfish and saxitoxin in shellfish, which pose serious food poisoning risks **(Bane et al., 2014).** Regulatory agencies, including the U.S. Food and Drug Administration (FDA) and European Food Safety Authority (EFSA), have established stringent screening protocols for detecting these toxins in edible products **(Jiang et al., 2023).** Environmental matrices, such as water, soil, and forensic crime scene residues, are also critical for venom detection in cases where toxins are dispersed through secondary contamination. In marine environments, monitoring for dinoflagellate-produced saxitoxins is essential to prevent harmful algal blooms from contaminating drinking water and seafood supplies (Deshwal et al., 2021). Effective venom detection depends on the selection of the appropriate matrix, followed by specialized extraction and quantification techniques **(Fischer et al., 2024).**

* **Extraction Techniques**

The extraction of venom toxins from complex biological and food matrices is a crucial step that directly influences the accuracy of toxin identification and quantification. The choice of extraction technique depends on the chemical nature of the venom component, such as whether it is a proteinaceous enzyme, a peptide-based neurotoxin, or a low-molecular-weight alkaloid toxin **(Kini & Koh, 2020)**. Advanced extraction methods have been developed to isolate and concentrate venom compounds while preserving their structural integrity **(Bane et al., 2014).**

One of the most widely used extraction techniques is solid-phase extraction (SPE), which is particularly effective for isolating low-molecular-weight neurotoxins such as tetrodotoxin and saxitoxin from serum, urine, and seafood samples **(Hagen et al., 2021).** This method utilizes selective adsorption of toxins onto a solid phase (e.g., silica or C18 cartridges), followed by elution with organic solvents, ensuring high recovery rates and sample purity **(Jiang et al., 2023).** For proteinaceous venoms, ultrafiltration and dialysis are commonly employed to separate large venom proteins from small toxic peptides, which is particularly useful in the analysis of snake venom phospholipases and scorpion neurotoxins **(Chen et al., 2022).**

Liquid-liquid extraction (LLE) is another widely used method for extracting lipophilic venom alkaloids, such as batrachotoxin from poison dart frogs. It exploits the differential solubility of toxins in aqueous and organic solvents, allowing for efficient separation and purification **(Bane et al., 2014).** Additionally, immunoaffinity chromatography (IAC) has gained prominence for its ability to selectively capture specific venom proteins using antibody-based binding systems. This technique is extensively used in clinical diagnostics and forensic toxicology, where targeted venom detection is required **(Kini & Koh, 2020).** The continuous refinement of extraction techniques is crucial for improving sensitivity, reducing sample complexity, and ensuring the reliability of venom detection assays **(Fischer et al., 2024).**

* **Quantification Using Analytical Techniques**

After extraction, venom toxins must be precisely quantified to determine their concentration, toxicity levels, and forensic significance. The most commonly used analytical methods include liquid chromatography-mass spectrometry (LC-MS/MS), high-performance liquid chromatography (HPLC), gas chromatography-mass spectrometry (GC-MS), enzyme-linked immunosorbent assay (ELISA), and nuclear magnetic resonance (NMR) spectroscopy (Deshwal et al., 2021). Among these, LC-MS/MS is considered the gold standard due to its high specificity, sensitivity, and ability to detect toxins at picogram levels (Hagen et al., 2021). It is particularly useful for identifying tetrodotoxin, saxitoxin, and batrachotoxin in biological fluids and food samples **(Bane et al., 2014).**

HPLC remains a widely used method for quantifying venom alkaloids and protein toxins, offering high separation efficiency and reproducibility **(Chen et al., 2022).** It is frequently used in food safety testing to screen for tetrodotoxin contamination in seafood **(Jiang et al., 2023).** In contrast, GC-MS is preferred for detecting volatile venom components, such as hydrogen cyanide and cyanogenic glycosides. This technique is extensively used in forensic toxicology to confirm cyanide poisoning cases **(Kini & Koh, 2020).**

For protein-based venom toxins, ELISA assays are commonly used due to their high-throughput capability and specificity **(Deshwal et al., 2021).** This method employs antibody-antigen interactions to detect venom proteins from snakes, scorpions, and wasps in clinical samples **(Fischer et al., 2024).** However, it is limited by lower sensitivity compared to mass spectrometry-based methods **(Chen et al., 2022).** Nuclear magnetic resonance (NMR) spectroscopy is increasingly being explored for its ability to characterize venom toxin structures and study toxin-receptor interactions, particularly in drug discovery research **(Hagen et al., 2021).** The selection of the appropriate analytical method depends on the type of venom, the required detection sensitivity, and the application—whether forensic, clinical, or environmental monitoring **(Jiang et al., 2023).**

* + 1. **Medical and Biotechnological Applications of Venom-Derived Toxins**

Venom-derived toxins, once considered solely as lethal biochemical agents, have garnered significant attention in modern medicine for their potential therapeutic applications. These toxins exhibit remarkable specificity in targeting biological pathways, making them valuable candidates for drug development. Their ability to modulate ion channels, enzymes, and receptors has led to breakthroughs in **pain management, antimicrobial therapy, and cardiovascular medicine**. This section explores some of the most promising venom-based compounds currently being investigated for medical use.

* **Tetrodotoxin: A Potential Painkiller for Chronic Pain Management**

Tetrodotoxin (TTX), a potent sodium channel blocker found in pufferfish, blue-ringed octopuses, and certain amphibians, is being actively researched as a non-opioid analgesic. Unlike conventional painkillers, particularly opioids, TTX does not induce addiction or respiratory depression, making it an attractive alternative for managing neuropathic pain, cancer pain, and opioid-resistant pain. The toxin works by selectively binding to voltage-gated sodium channels (Nav1.7, Nav1.8, and Nav1.9), which are responsible for pain signal transmission. By preventing nerve depolarization, it effectively blocks pain at its source, offering sustained relief for chronic conditions.

Several clinical trials have demonstrated the potential of TTX in treating chemotherapy-induced neuropathic pain and diabetic neuropathy. In Phase II and III trials, patients receiving TTX reported significant reductions in pain levels compared to conventional treatments **(Hagen et al., 2021).** Furthermore, ongoing research is focused on developing TTX derivatives with improved safety profiles, allowing for broader clinical applications. Despite its promise, precise dosage control is crucial, as TTX is highly toxic at higher concentrations. Future studies are aimed at refining delivery mechanisms to maximize its analgesic potential while minimizing toxicity **(Bane et al., 2014).**

* **Mastoparan and Antimicrobial Peptides in Antibiotic Development**

With the rise of antibiotic resistance, researchers have turned to venom-derived antimicrobial peptides (AMPs) as alternatives to traditional antibiotics. One of the most promising candidates is mastoparan, a cationic antimicrobial peptide derived from wasp venom. Unlike conventional antibiotics, which often face bacterial resistance, mastoparan exerts its antimicrobial effects by destabilizing bacterial membranes, leading to rapid cell lysis. This mechanism is particularly effective against multi-drug-resistant (MDR) bacteria, including methicillin-resistant Staphylococcus aureus (MRSA) and Pseudomonas aeruginosa **(Jiang et al., 2023).**

Recent studies have explored the synergistic effects of mastoparan when used in combination with existing antibiotics. Research indicates that mastoparan enhances membrane permeability, allowing antibiotics to penetrate bacterial cells more effectively **(Chen et al., 2022).** This property makes it a valuable adjuvant therapy, potentially restoring the efficacy of antibiotics that have become less effective due to resistance. Additionally, mastoparan is being investigated for its role in wound healing, particularly in cases of diabetic ulcers and infected wounds. The development of mastoparan-based antimicrobial gels has shown promising results in accelerating tissue regeneration and preventing infections **(Fischer et al., 2024).** As research progresses, efforts are being made to synthesize less toxic analogs of mastoparan to ensure safety and stability for medical use.

* + 1. **Case studies**
* ***Case study 1: Cantharidin poisoning***

Following three days of rigorous physical training and a water intake of less than 600 millilitres per day, a 23-year-old male soldier chewed and swallowed a toxic beetle (Berberomeloe majalis) as part of a wager. He had vomiting, dysuria, hematuria, mouth burning, and abdominal pain within 15 minutes. Upon arrival at the hospital, he displayed elevated leukocytes, azotemia, high LDH and CK, proteinuria, glycosuria, hematuria, and was dehydrated, hypotensive (98/53 mmHg), and mildly tachycardic (37.8°C).After receiving supportive care, saline, and antibiotics, his azotemia worsened, and he was transferred to nephrology. Dehydration, cantharidin toxicity, and rhabdomyolysis were linked to the diagnosis of multifactorial acute kidney injury (AKI). Leptospirosis was taken into account but excluded. He experienced polyuria and renal recovery in a matter of days after receiving ceftriaxone therapy and intense hydration. After 15 days, his full recovery was confirmed, and he was released asymptomatic on day seven **(Cotovio et al., 2013).**

* ***Case study 2: Tetrodotoxin poisoning***

After eating dried fish they bought from a street vendor in New York City, a 30-year-old man and his 33-year-old sister arrived at the emergency department (ED) with suspected puffer fish poisoning.

They reported symptoms such as fatigue, dyspnea, perioral numbness, and weakness in their extremities thirty minutes after consumption. Similar symptoms were reported by two other people who consumed the fish, but they chose not to seek medical attention. With the exception of the man's mild tachypnea and elevated blood pressure, which went away after six hours of observation, the patient's vitals were stable. With a few minor electrolyte abnormalities, the laboratory results were generally normal. The fish, identified as Lagocephalus lunaris, had high levels of tetrodotoxin, with concentrations ranging from 5.7 to 72.3 ppm, according to genetic and toxin analyses. Both patients left the emergency department against medical advice, making follow-up impossible, and the source of the fish could not be identified despite efforts by law enforcement and public health. **(Tetrodotoxin Poisoning Outbreak From Imported Dried Puffer Fish — Minneapolis, Minnesota, 2014, 2015)**

1. **Discussion**

Toxins secreted by animals and insects play critical roles in their survival, either as a defense mechanism or for predation. These biochemical substances demonstrate remarkable diversity in their modes of action and physiological effects.
Recent additions to this review include insect-derived toxins, such as cantharidin from blister beetles and mastoparan from wasps. These substances exhibit unique mechanisms, with cantharidin causing blistering and renal damage, and mastoparan disrupting cellular membranes. The inclusion of insect-derived toxins broadens the understanding of zootoxins, highlighting their evolutionary adaptations and ecological significance. For instance, cantharidin is a mating gift in blister beetles, while mastoparan serves as a colony defense mechanism in social wasps. These examples underscore the versatility of insect toxins.

Animal toxins, such as batrachotoxin and tetrodotoxin, primarily target neural pathways, often leading to paralysis or fatal systemic effects. In contrast, insect toxins like platytoxin and butylidenephthalide exhibit antimicrobial and neurotoxic properties, with potential applications in pest management and medicine. This comparative analysis demonstrates that while animal toxins frequently involve sophisticated sodium or potassium channel modulation, insect toxins reveal novel pathways for chemical defense and interaction with predators or prey. The integration of toxins from both animals and insects provides a foundation for innovative research into therapeutic and industrial applications. For example, the antimicrobial properties of butylidenephthalide secreted by Lucilia sericata larvae have been leveraged in medical maggot therapy. Similarly, tetrodotoxin's potential as a cancer therapy is under investigation. However, significant challenges remain in the detection and neutralization of these potent substances. Advances in analytical techniques, such as liquid chromatography-mass spectrometry, are vital for understanding toxin pathways and developing effective treatments. Understanding the molecular evolution of these toxins and their ecological roles is essential for developing innovative applications and antidotes. Interdisciplinary research integrating toxicology, pharmacology, and entomology is necessary to bridge gaps in knowledge, particularly concerning lesser-known insect and animal toxins.

1. **CONCLUSION**

In conclusion, This review comprehensively explores the toxins and poisons secreted by venomous and poisonous animals and insects. These substances demonstrate diverse mechanisms, such as blocking sodium channels, disrupting cell membranes, and inducing neurotoxic or hemolytic effects. Despite their potential lethality, many toxins hold promise for therapeutic applications, including antimicrobial agents, cancer treatments, and neurotoxin-based therapies. However, the absence of antidotes for most of these toxins and challenges in their detection highlight critical gaps in research. Future efforts must focus on understanding their molecular mechanisms, improving diagnostic tools, and developing antidotes, advancing their utility while mitigating risks.

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1. Quill Bot for Paraphrasing.

2.

3.

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