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MEDICINE REVIEW

The biological and medical significance of poisonous animals

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ABSTRACT

Animal kingdom possesses numerous poisonous species that produce venoms (actively delivered) or toxins (passively delivered). Poisonous animals are found in most classes of the Animal Kingdom and in most habitats, both terrestrial and marine. Poisonous animals have a significant health problem for populations in the world and are neglected environmental diseases of the rural tropics. Poisonous animals include a variety of animal species; sea snakes, stinging fish, jellyfish, corals, cone shells, blue-ringed octopuses, sea urchins, snakes (elapids, vipers, and rattlesnakes), scorpion, spiders, bee, wasp and ant. Poisonous animal are rich sources of toxins that often target-with high potency and variable specificity. Animal toxins have made a significant contribution to enhancing knowledge in human physiology and pharmacology. Information on the nature and mechanism of action of these toxins has enabled a more scientific approach to the treatment of their intoxications. This paper reviews the knowledge about the various aspects related to the name, habitat, biological and medical importance of poisonous animals of different major animal phyla. In addition, this review will discuss the mechanism of venoms or toxins toxicity and therapeutic uses of particular fractions of venoms or toxins from different sources.

Key words: Poisonous animals; Scorpion; Snake; Spider; Jelly fish; Octopus; Venoms; Neurotoxin; Conotoxin; Tetrodotoxin; Phospholipase A.

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INTRODUCTION

Animal venoms and toxins are now recognized as major sources of bioactive molecules that may be tomorrow's new drug leads. Venom is a secretion produced in a specialized gland in one animal and delivered to a target animal through the infliction of a wound. This secretion must contain molecules that disrupt normal physiological processes [1]. Venoms may be used to kill prey and/or to defend the delivering organism against attack by predators. Venoms are complex mixtures of pharmacologically highly active substances and can cause a wide range of symptoms [2].

The venom which contains mucopolysaccharides, hyaluronidase, phospholipase, serotonin, histamine, enzyme inhibitors, and protein is namely neurotoxic peptide (Table 1) [3, 4]. The neurotoxic peptides are responsible for the symptoms that present during envenomation by interacting with ion channels and have the potential to cause massive damage to nervous system of both vertebrates and invertebrates [5]. Pre-synaptic neuromuscular junction neurotoxins act at the neuromuscular junction, damaging the terminal axon followed by cessation of all neurotransmitter release and irreversible paralysis. Post-synaptic toxins act by reversible binding to the acetylcholine receptor on the skeletal muscle end plate. Tetrodotoxin found in saliva of the Australian blue ringed octopus and the flesh of puffer fish causes rapid and reversible paralysis of skeletal muscle by blocking nerve transmission through action on the sodium channels of axons. A variety of potassium channel blocking toxins exist in the venoms of some scorpion and cone shell. Some snake venoms contain myolysins which caused myolysis of skeletal muscles, however, cardiac effects are prominent in envenoming by scorpions, jellyfish and cone shells.

Some venoms contain true anticoagulants components that directly inhibit portions of the clotting cascade resulting in prolonged clotting times (Table 2). The viperid zinc metalloproteinases causes capillary leakage resulting in haemorrhagic necrosis. Renal damage may follow envenoming by a wide range of venomous animals as a secondary effect of venom induced hypotension. Some snakes e.g vipers, pit vipers, cobras commonly cause major local tissue injury, as a result of cytolytic phospholipase A2 toxins. A few spiders cause local necrosis as the most prominent feature of envenomnation [6, 7].

Venom allergens cause immunostimulation of body tissues and show strong T cell responses in hypersensitive patients and signify the production of allergen specific IgE antibodies and generate anaphylactic reactions. Generally, venom toxins make fast release of certain chemicals i.e. serotonins, kinins, prostaglandins and leukotrienes that results in visible clinical symptoms related to paralysis, inflammation, swelling and itching [8].

Table 1. Major venomous animal groups commonly associated with neurotoxic paralysis [9].

Type of animal	Examples	Type of neurotoxin
Elapid snakes	Kraits	Pre- and postsynaptic
	Coral snakes	Postsynaptic
	Mambas	Dendrotoxins and fasciculins
	King cobra	Postsynaptic
	Selected Australian snakes; tiger snakes, taipans, rough scaled snake, death adders, copperheads	Pre- and postsynaptic
	Sea snakes	Postsynaptic
Viperid snakes	Mohave rattlesnake	Presynaptic
	Neotropical rattlesnakes	Presynaptic
	Sri Lankan Russell's viper	Postsynaptic
Ticks	Paralysis ticks, *Ixodes* and *Dermacentor* spp.	Presynaptic
Cone shells	Variety of *Conus* spp.	Conotoxins
Octopusses	Blue ringed octopuses, *Hapalochlaena* spp.	Tetrodotoxin

REVIEW

1. Phylum Protozoa

Dinoflagellates, unicellular marine protozoons, produce some of the largest and most complex polyketides identified to date. The biological activities of these molecules are quite diverse [11].

2. Phylum Porifera

Sponges are simple multicellular animals, living mainly in shallow coastal and fresh waters around the world. They either attach to rock, seaweed or a hard-shelled animal or burrow into calcareous shells or rock. Most sponges are harmless to humans, while a few venomous species exist that have tiny spicules made of silicon can penetrate the skin and deliver venom. The effect of picking up a venomous sponge is not immediate but some time after the contact the area of skin touched becomes red and swelled with severe pain for days or even weeks. Moreover, the external surface of some species of sponges has small perforations from which chemical substances or crinitoxins are extruded. Three species including the red-beard sponge (*Micronia prolifera*), fire sponge (*Tedania ignis*) and poison-bun sponge (*Fibulila* sp.) causes dermatitis [12].

The majority of sponge glycosides were isolated from sponges belonging to species of orders Astrophorida and Poecilosclerida. The distribution and biological activities of these compounds suggest their parallel origin and evolution as defensive agents in several taxa of the class. Chemically, these compounds are very diverse and quite different in the structures of the both aglycone and carbohydrate moieties, when compared with other glycosides of marine or terrestrial origin. Sponge glycosides demonstrate antiprotozoal, antifungal and antitumor activities [13]. Moreover, marine sponges produce vast range of antitumor, antiviral, antiinflammatory, immunosuppressive, antibiotic, and other bioactive molecules that can

Table 2. Major venomous animal groups expected to cause primary coagulopathy [10].

Type of animal	Examples	Type of venom action
Colubrid snakes	Boomslang, vine snake Yamakagashi, red necked keelback	Procoagulant
Elapid snakes	- Selected Australian snakes; tiger snakes, rough scaled snake, taipans, brown snakes, broad headed snakes - Selected Australian snakes; mulga snakes, Collett's snake, black snakes, Papuan black Snake	- Procoagulant - Anticoagulant
Viperid snakes	- Saw scaled or carpet vipers - Gaboon vipers and puff adders - Russell's vipers - Malayan pit viper - North American rattlesnakes - North American copperheads - South American pit vipers (selected *Bothrops* spp.) - Asian green pit vipers (selected *Trimeresurus* spp.) - EuroAsian vipers (selected *Vipera* spp.)	- Procoagulant, disintegrins, haemorrhagins - Procoagulant, antiplatelet, disintegrins, haemorrhagins - Procoagulant, haemorrhagins - Procoagulant, antiplatelet, haemorrhagins - Procoagulant, fibrinolytic, antiplatelet, disintegrins, haemorrhagins - Procoagulant, anticoagulant, fibrinolytic, disintegrins - Procoagulant, Anticoagulant, fibrinolytic, disintegrins, haemorrhagins - Anticoagulant, fibrinolytic, antiplatelet, haemorrhagins - Procoagulant, disintegrins, haemorrhagins,
Insects	Latin American caterpillars, *Lonomia* spp.	Procoagulant

affect the pathogenesis of many human diseases. The relationship between the chemical structures of the secondary metabolites from sponges and the diseases they affect is not clear. However, different components affect the targeted disease through microtubule stabilization or interaction with DNA to combat tumors. Also, most bioactive metabolites from sponges are inhibitors of certain enzymes, which often mediate or produce mediators of intracellular or intercellular messengers that are involved in the pathogenesis of a disease. The potency of sponge-derived medicines lies in the fact that each of these thousands of metabolites and their derivatives has its own specific dose-related inhibitory effect, efficacy, and potential side effects [14].

Halichondrin B was initially purified from the sponge *Halichondria okadai* in Japan and has shown in vivo activity in melanoma and leukaemia models. It can also be obtained from the deep-water sponge *Lissodendoryx*, which is found in New Zealand. This compound is also active in various human tumour-cell models in vitro and in vivo and appears to interfere with microtubule function [15]. New bisindole alkaloids of the topsentin and hamacanthin classes have been isolated from the Mediterranean sponge *Rhaphisia lacazei* showed significant antiproliferative activity against a series of human cell lines in vitro [16]. Moreover, initial studies on sesquiterpenes, parahigginols, and parahigginic acid isolated from a Taiwanese marine sponge *Parahigginsia* sp. revealed that these compounds were cytotoxic against tumour cells [17].

3. Phylum Cnidaria

Cnidarians are relatively simple radially symmetrical body. Their body cavity has a single opening surrounded commonly by tentacles equipped with special cells known as cnidocytes. Cnidarians are separated into four groups: the Hydrozoa (plume-like hydroids, medusae and Siphonophora), Scyphozoa (free-swimming jellyfish), Cubozoa (box-shaped medusae) and Anthozoa (hard and soft corals and anemones). Hydroids and jellyfish possess nematocysts, on the other hand sea anemones and true corals have spirocysts with adhesive cnidae threads [18, 19].

Cnidarian venoms are contained in the nematocysts secreted by the Golgi apparatus of nematoblasts, the cells specialized for this function. The nematocysts contain a tightly spiralized and differently shaped thread, which according to the species, is provided with spines and with a basal enlarged portion known as the 'shaft'; after mechanical or chemical stimulation, the thread is averted, injecting the venom contained into the capsule [20].

Nematocyst in the tentacles of the sea anemone contains a coiled hollow filament containing a potent toxin affecting voltage gated Na^+ and K^+ channels, acid-sensing ion channels, actinoporins and protease inhibitors [21-23]. Actinoporins are highly toxic to fish and crustaceans, which may be the natural prey of sea anemones. In most cases, a sting by the nematocysts causes local inflammations, pain and edema [24]. Toxin from sea anemone is potently inhibits T-lymphocyte proliferation in models of certain autoimmune diseases [25]. All species of jellyfish in the Mediterranean are relatively harmless; however, *Pelagia noctiluca*, *Chrysaora hysoscella* and *Rhopilema nomadica* are considered the most venomous [26]. The delayed jellyfish envenomation syndrome with serious multiple organ dysfunction or systemic damages developed after jellyfish stings may be attributed to the synergy of cytotoxicity, vasoconstriction effect and other specific target organ toxicities of jellyfish venom [27].

Some bioactive substances were discovered in cnidarians, such as prostaglandins (PGA2) in the gorgonian *Plaxaura homomalla* [28], Palytoxin local anaesthetic and vasoconstrictive agent and induce ion currents in mouse neuroblastoma cells discovered in the zoanthid *Palythoa toxica* [29, 30]. Cytolytic and antitumoral prostanoid compounds from the Anthozoan *Clavularia viridis* were shown to inhibit the growth of HL-60 leukemic cells [31]. Moreover, the incidence and growth of tumors induced by N-Ethyl-N-Nitrosourea were affected by the crude venom of the scyphozoan *Cassiopea xamachana* [32] and the growth of Ehrlich ascites tumors grafted in mice was inhibited by crude extracts of jellyfish and soft corals [33]. Also, equinatoxin extracted from *Actinia equina* showed antitumoral activity on cultured cells [34].

4. Phylum Arthropoda

Basically according to Koehler and Diclaro [35] venomous arthropods produce venoms that can be classified as; venoms that produce blisters (e.g., blister beetles, certain stinging caterpillars, millipedes), venoms that attack the central nervous

system (e.g., black and brown widow spiders, bark scorpions, certain ticks, Hymenoptera, wheel bugs), venoms that destroy tissue, or cytolytic and hemolytic toxins (e.g., Hymenoptera, fire ants, ground scorpions, mites, chiggers, wheel bugs, brown recluse spider), venoms that prevent blood from clotting, or hemorrhagic toxins (e.g., lice, fleas, ticks, mites, true bugs, biting flies).

4a. Class Insects

Venomous insects are known from the orders Lepidoptera, Hemiptera, and Hymenoptera [36]. The method of delivery may be active, such as the sting apparatus of Hymenoptera (bees and wasps), and the mouthparts of Hemiptera (stylets), or passive such as the modified setae in some lepidopteran larvae (caterpillars). Hymenopterans are insects that inject venom with a stinging apparatus connected to venom glands in the terminal part of the abdomen. Some species of ants lack a sting and instead spray their venom. Honeybees and wasps are widely and numerously distributed in cold and tropical climates; therefore, most humans experience multiple stings during a lifetime. Single stings are dangerous for people who are allergic to the venom. Direct toxic effects, as opposed to allergic reactions account for 15% of all deaths caused by hymenopteran stings [37].

Insect venom is a poisonous substance that contains a complex mixture of certain proteins, enzymes, small peptides, certain inorganic elements and acids. These venom components are responsible for multiple pharmacological effects in different organisms. These venoms act at cellular level and break the normal barrier to leak out molecules across the cell membrane and form ion channels by attaching themselves to the membrane surface. Insect venom toxins elevate the level of blood sugar, lactate, glucagon and cortisol and cause massive destruction of erythrocytes and nerve cells. In addition, insect venom possess highly potent short peptides act on ion channels of excitable cells and inhibit the activity of important metabolic enzymes. Melittin is a short peptide that shows cytotoxicity and cause intravascular hemolysis of erythrocytes, leucocytes, platelets and vascular endothelium. It is highly basic peptide that inserts itself into the phospholipid bi-layer of cell membranes [8].

Venom secreted from the salivary glands of ticks during the blood meal is absorbed by the host and systemically distributed. Paralysis results from the ixovotoxin, very similar to botulinum toxin due to inhibition of the acetylcholine release at the neuromuscular junction and autonomic ganglia [38, 39]. Both ixovotoxin and botulinum toxin demonstrate temperature dependence in rat models and shows increased muscular twitching activity as the temperature is reduced [40]. The antimicrobial venom peptides of honey bee *Apis mellifera* are present on the cuticle of adult bees and on the nest wax. It has been suggested that these substances act as a social antiseptic device. Venom functions are well beyond the classical stereotype of defense against predators, and the different nesting biology of these species may be related to the use of the venom in a social immunity context [41]. Bumblebee venom contains a variety of components, including bombolitin, phospholipase A2, serine proteases, and serine protease inhibitors. A bumblebee (*Bombus terrestris*) venom serine protease inhibitor that acts as a plasmin inhibitor was consists of a 58-amino acid mature peptide that displays features consistent with snake venom Kunitz-type inhibitors, including six conserved cysteine residues and a P1 site [42]. *Solenopsis* fire ants are native to the Americas, with most of the species occurring in lower regions of South America [43]. Fire ant venom includes more than 95% piperidinic alkaloids and less than 5% aqueous fraction of allergenic proteins [44, 45].

4b. Class Arachnida

From the venom of arachnids (scorpion and spiders) several hundred peptides have been isolated and characterized, most of which are relatively short peptides that interfere with cellular communication and impair proper function. Cloning genes extracted from the venomous glands of arachnids is revealed thousands of novel sequences [46]. Spiders employ venom jaws that are connected to venom glands to catch prey and for use in self defense. Most spiders either have venom jaws that are too small to penetrate human skin or their venom is too weak to produce substantial envenoming. Spider bites may go unnoticed until clinical signs and symptoms develop. Systemic neurotoxic envenoming is caused by widow spiders (*Latrodectus* sp.), wandering spiders (*Phoneutria* sp.), and funnel web spiders (*Atrax* sp. and *Hadronyche* sp.) are resembles envenoming from scorpion stings. The

clinical course of envenoming by these spiders is also predominantly triggered by catecholamine release [3, 47, 48]. Over a period of more than 300 million years, spiders have evolved an extensive library of bioactive peptides. Moreover, in contrast with man-made combinatorial peptide libraries, spider-venom peptides have been pre-optimized for high affinity and selectivity against a diverse range of molecular targets. It is therefore not surprising that numerous spider-venom peptides have been characterized that potently and selectively modulate the activity of a diverse range of therapeutic targets [49].

Spider venoms are complex mixtures of neurotoxic peptides, proteins and low molecular mass organic molecules. Their neurotoxic activity is due to the interaction of the venom components with cellular receptors in particular ion channels. Spider venoms have proven to be a rich source of highly specific peptide ligands for selected subtypes of potassium, sodium and calcium channels, and these toxins have been used to elucidate the structure and physiological roles of the channels in excitable and non-excitable cells [50-52].

The Brazilian tarantula *Acanthoscurria paulensis* venom induced many behavioral and physiological changes in mice. An inotropic effect produced on frog heart is probably due to the low molecular mass compounds present in the more hydrophilic fractions of venom that may act either by inducting the release of acetylcholine from parasympathetic terminals or by directly acting as a cholinergic agonist [53].

Loxoscelism is a set of signs and symptoms caused by the bite of spiders of the genus *Loxosceles* [54]. *Loxosceles* (Araneae, Sicariidae) can be found in temperate and tropical regions of America, Oceania, Asia, Africa and Europe [55, 56]. This genus represents a public health problem in Brazil, mainly in South and Southeast regions, with more than 3000 cases reported annually by the Ministry of Health [52]. Usually, the clinical manifestations of loxoscelism are characterized by necroulcerative dermatitis at the site of the bite. However the envenoming can also cause systemic effects leading to acute renal failure, which may be lethal [52, 57, 58]. Locally, lesions caused by loxosceles venom present edema, hemorrhage, inflammation with dominance of neutrophils, rhabdomyolisis, damage to the vessels wall, thrombosis, and dermonecrosis [59, 60]. Recently, by using a cDNA library and transcriptome analysis, a novel expression profile has been elaborated for *Loxosceles intermedia* gland venom. This recently developed profile has allowed the identification of additional toxins as components of the venom, including insecticidal peptides similar to knottins, astacin-like metalloproteases, venom allergen, a translationally controlled tumor protein family member, serine protease inhibitors, and neurotoxins similar to Magi 3 [61, 62]. In addition, the biotechnological use of *Loxosceles* toxins could provide information related to the tridimensional structure of identified toxins, through crystallography and X-ray diffraction and/or nuclear magnetic resonance for soluble toxins [63], from such data, synthetic ligands, analogs, or inhibitors could be designed for biotechnological purposes [64].

Scorpions are found in all the world causes problems in tropical and subtropical regions. Travelers are stung when they accidentally squeeze scorpions that are hiding in beds, luggage, shoes, and clothing [65]. Scorpions are actually very beneficial to ecosystems because they eat insects, spiders, centipedes and even other scorpions. In turn, they provide an important food source for large centipedes, tarantulas, snakes, some lizards, birds, bats, and other small mammals. Scorpion venom varies from species to species, but generally consists of different mixtures of neurotoxins [66].

Scorpion toxins are classified according to their structure, mode of action, and binding site on different channels or channel subtypes [67]. The long chain toxins affecting sodium channels have been subdivided primarily into two major subtypes, α- and β-toxins [68]. The α-toxins bind to receptor site 3 of the voltage-gated Na^+ channels of vertebrates in a membrane-dependent manner [69]. The major effects of α-toxins induce a prolongation of the action potential of nerves and muscles by fast inactivation of sodium channels receptor affinity dependent upon membrane potential [67, 70]. The β-toxins are isolated from American scorpions, bind to receptor site 4 on vertebrate Na^+ channels and producing a shift to amore negative membrane potential [71, 72]. So, Scorpion β-toxins have been used as pharmacological tools in the study of voltage-activated Na^+ channels [51].

Systemic envenoming is caused by members of the genera *Centruroides*; *Tityus*; *Androctonus*, *Buthus*, *Leiurus*, *Nebo*; *Hemiscorpius*; *Parabuthus*; and *Mesobuthus* [2]. Local envenoming causes

pain, erythema, and swelling. Systemic envenoming usually develops in two phases: a cholinergic phase involving vomiting, sweating, hypersalivation, priapism, bradycardia, and arterial hypotension, followed by an adrenergic phase involving arterial hypertension, tachycardia, and cardiac failure. Cranial nerves and neuromuscular junctions and respiratory organs may be affected [73]. The mediators affecting inflammatory processes may be released after scorpion envenomation including kinins, ecosanoids, platelet activating factor, nitric oxide, and cytokines [74]. A total of 74 fractions were separated from the Urodacidae scorpions, the most widely distributed in Australia, allowing the identification of approximately 274 different molecular masses with molecular weights varying from 287 to 43.437 Da. The most abundant peptides were those from 1 kDa and 4–5 kDa representing antimicrobial peptides and putative potassium channel toxins, respectively. The transcriptome analysis of the venom glands of the same scorpion species, resulting cDNA library 172 expressed sequence tags [75].

5. Phylum Molusca

The most important venomous mollusks are from the Gastropoda and Cephalopoda classes. Gastropoda (genus *Conus*) contain mollusks able to envenom prey and occasionally even Man. Octopus vulgaris is a common marine animal that can be found in nearly all tropical and semitropical waters around the world. *Octopus vulgaris* bite resulting in an ulcerative lesion with slow wound healing owing to *P. oryzihabitans* infection [76]. The blue-ringed octopus (*Hapalochlaena maculata* and *Hapalochlaena lunulata*) inoculates maculotoxin from their saliva glands through their horny beak. Recently maculotoxin was demonstrated as identical to tetrodotoxin [77]. Tetrodotoxin is a potent neurotoxin that blocks axonal sodium channels and provokes a muscular paralysis similar to that observed in accidents with *Conus* shells including fatal respiratory arrest [78]. Mollusks of the genus *Conus* present a venomous apparatus composed of radulae, a chitin structure linked to glands, which injects potent neurotoxic peptides, conotoxins, causing serious human envenomation that is associate with the blockage of certain receptors and muscular paralysis [79]. The venom from any one *Conus* species contains a large number of peptides. Every conotoxin serves as a highly specific ligand, each with a particular molecular target. Binding of the peptide ligand to its target leads to a biologically relevant change in physiological function [80]. Currently, conotoxins are a valuable tool of scientific research due to the intense pharmacological activity presented by the peptides. One of the drugs in clinical tests is ziconotide which is a peptide that blocks the neuronal calcium canals with excellent effect in the treatment of chronic and severe painful processes [81]. Moreover, conotoxins from different super-families were commonly found to have similar distributions. A new conotoxin, PCCSKLHDNSCCGL was sequenced [87]. Conotoxins composed mostly of 100–250 disulfide-bridged peptides are synthesized in the epithelial cells of the venom duct, then secreted in discrete parts of the same duct, a convoluted gland often several centimeters long [83]. Conotoxins bind to receptors such as voltage- and ligand-gated ion channels, G-protein-coupled receptors, and neurotransmitter transporters in the muscular and nervous system [84].

Conotoxins provide a vast library of peptides with unique abilities to discriminate among types and subtypes of ion channels in a manner that is unmatched by the typical small molecule drugs which dominate the pharmaceutical industry. In addition, cone venom peptides are small and inherently stable, making them ideal leads for peptide therapeutics, especially ion channel therapeutics. The high structural resolution now obtained with modern NMR spectroscopy and X-ray crystallography provides emerging opportunities to use conotoxins as templates for the design of smaller peptidomimetics that incorporate the selectivity and potency of conotoxins. Because of its selectivity and potency, w-conotoxin MVIIA (Ziconotide) is being developed as a drug for the treatment of chronic pain. With improvement in methods of delivering peptides, it is anticipated that conopeptides can be modified for effective oral delivery [85]. The purified peptide from crassispirids venom of marine gastropods has 29 amino acid residues long, with the sequence: GSCGLPCHEN-RRCGWACYCDDGICKPLRV [86].

6. Phylum Echinodermata

Generally, some species of echinodermata are poisonous some of them are venomous. The venomous species inject their toxin into the victim through spines or other similar structures. The

poisonous species contain poison within their tissues which affect the victim when consumed. The venomous species can be consumed after being cooked, but poisonous species should never be consumed as the poison will not be inactivated even by the high temperature of cooking also [87]. *Globiferous pedicellariae* or *Sphaerechinus granularis* are venomous defensive appendages consisting of a stalk bearing a head made of three movable jaws. Each jaw is supported by a calcareous valve ending with a terminal grooved tooth. The venom apparatus is located in each jaw and consists of a venom gland surrounded by a muscular envelope and terminating in a duct which completely encircles the terminal tooth of the valve. In mature pedicellariae the venom is stored in intracellular vacuoles of highly differentiated cells. Upon contraction of the muscular envelope the venom is released via a holocrine mechanism and infiltrates the predator's tissues through the wound inflicted by the three calcareous teeth of the valves [88].

7. Phylum Vertebrata

7a. Class Fishes

Venomous fish stings are a common environment hazard worldwide. Venomous fish carry venom gland bearing fin rays for self defense. The venom glands are located mainly in the dorsal fins, but they can be found in the ventral and anal fins as in scorpion fish, lion fish, and stone fish or in the dorsal and pectoral fin as in catfish-mostly freshwater species. Stingrays have one or more serrated stings located on their whip-like tails. Fresh water stingrays are found in rivers and lakes in South America and Africa. Weever fish of the Mediterranean and Eastern Atlantic coastal waters and toad fish possess venomous stings on their gill covers and in the dorsal fins [19, 47]. Stings from venomous fish cause agonizing pain and mechanical injury that destroys tissue. In rare instances, deeply penetrating stings can affect large blood vessels and major nerves. Some species of venomous fish can cause systemic envenomination [6, 47, 89]. Venoms from stonefish (genus *Synanceja*) have marked effects on the cardiovascular and neuromuscular systems, vascular perpeability and exhibit haemolytic and hyaluronidase activity [4]. Venomous fish are often involved in human accidents and symptoms of envenomation include local (intense pain and swelling) and systemic effects (cardiovascular and neurological disorders). Stonefish antivenom evoked an immune cross-reactive response with scorpionfish venom and is efficient in neutralizing the most prominent toxic effects of scorpionfish venom. This is in accordance with the hypothesis that venomous fish belonging to different genera or inhabiting different regions may share venom compounds with similar antigenic properties [90]. However the only commercially available antivenom is against the Indo-Pacific stonefish *Synanceja trachynis*. The venom similarities between Indo-Pacific and Atlantic venomous fish, suggested that the scorpionfish *Scorpaena plumieri* venom compound responsible for the inflammatory and cardiovascular effects [91].

Lionfish, members of the genera *Pterois*, *Parapterois* and *Dendrochirus* have venomous glandular tissues in dorsal, pelvic and anal spines. The lionfish toxins have been shown to cross-react with the stonefish toxins by neutralization tests using the commercial stonefish antivenom. Two species of *Pterois* lionfish (*P. antennata* and *P. volitans*) contain a 75 kDa protein cross-reacting with neoverrucotoxin. Then, the amino acid sequences of the *P. antennata* and *P. volitans* toxins were successfully determined by cDNA cloning using primers designed from the highly conserved sequences of the stonefish toxins. Remarkably, either a-subunits (699 amino acid residues) or b-subunits (698 amino acid residues) of the *P. antennata* and *P. volitans* toxins share as high as 99% sequence identity with each other. Furthermore, both a- and b-subunits of the lionfish toxins exhibit high sequence identity with each other and also with the b-subunits of the stonefish toxins [92].

7b. Class Amphibia

The amphibian skin contain various bioactive molecules that possess potential therapeutic activities like antibacterial, antifungal, antiprotozoal, antidiabetic, antineoplastic, alagesic and sleep inducing properties [93]. Frog skins alone have 24 different structural groups of 500 alkaloids [94]. The glanular skin gland secretions include amines, peptides, proteins, steroids, water soluble alkaloids and lipid-soluble alkaloids. The peptides include bradykinin, sauvagine, physaelaemin, caerulein, bombesin, dermorphins and adenoregulin [95]. Magainins are class of chemicals secreted by frogs

that are vasoactive peptides and has antibiotic properties that protect the skin [96], it work against bacterial and fungal pathogens by attacking their membranes, forming pores in the pathogens membrane that kill the organism [97]. The bufadienolides which are biosynthesized from cholesterol in the toads' diet are five times more deadly than the cardenolides. In vitro and animal models studies suggested that bufadienolides could be used clinically in place of, or in combination with cardenolides to improve treatment of congestive heart failure [98].

Chemical defense in a dendrobatid poison frog is dependent on geographic location and habitat type. A total of 232 alkaloids, representing 21 structural classes were detected in skin extracts from the dendrobatid poison frog *Oophaga pumilio* [99]. Lipid-soluble alkaloids that discovered in amphibian skin includes steroidal samandarines from salamanders, the batrachotoxins, histrionicotoxins, gephyrotoxins, and epibatidine from neotropical poison frogs, the pumiliotoxins, allopumiliotoxins, homopumiliotoxins, and decahydroquinolines from certain genera of anurans, and the pseudophrynamines from one genus of Australian frogs [100]. Bufadienolides are cardioactive steroids responsible for the anti-inflammatory actions of toad venom [101]. Venom of Bufo marinus toad contains a Na^+, K^+-ATPase inhibitor with potent vasoconstrictor activity [102].

Several studies describing the biochemical characterization of the components from the skin secretion of *Phyllomedusa* genus have allowed the identification of biologically active peptides that are very similar to the mammalian hormones, neuropeptides, as well as the broad-spectrum cytolytic antimicrobial peptides [103]. The antimicrobial peptides are grouped in seven families namely dermaseptins, phylloseptins, plasticins, dermatoxins, phylloxins, hyposins, and orphan peptides [104]. Some of these peptides; dermaseptins, phylloseptins, hyposins, and the bradykinin-related peptides were isolated and characterized from *Phyllomedusa hypochondrialis* skin secretion [96, 103-105]. The activity against grampositive and gram-negative bacteria, yeast and fungi were reported for dermaseptins [106], while antibacterial activity and antiparasitic activity against *Trypanosoma cruzi* were demonstrated for phylloseptins [107].

7c. Class Reptilia

No single characteristic distinguishes a poisonous snake from a harmless one except the presence of poison fangs and glands. The proteroglypha have in front of the upper jaw permanent erect fangs (fixed fangs), however, the solenoglypha have erectile fangs that can rise to an erect position (folded fangs). The fixed-fang snakes usually have neurotoxic venoms and the folded-fang snakes usually have hemotoxic venoms. However, the most poisonous snakes have both neurotoxic and hemotoxic venom. Of about 2000 different species of snakes, only 300 are venomous. Venomous snakes are found in the families Colubridae, Elapidae, Hydrophidae, Viperidae and Crotalidae. Over 95% of the dry weight of most venoms is polypeptide which includes enzymes, toxins and small peptides, each class being capable of modulating the physiological response of envenomed animals. More than 20 enzymes have been detected in snake venom and 12 are found in the majority of venoms. Hyaluronidase is present in all snake venoms facilitating the distribution of other venom components throughout the tissues of the prey [108].

Snake venoms are among the best pharmacologically characterized natural toxins chiefly because of their deleterious effects on humans. The most common classes of snake venom enzymes include phospholipase A2, phosphodiesterase, phosphomonoesterase, L-amino acid oxidase, specific endopeptidases, and nonspecific endopeptidases [109]. Snake venoms comprise a complex pool of proteins (more than 90% of the dry weight), organic compounds with low molecular mass and inorganic compounds [110-111]. Their quantitative and qualitative composition may vary according to factors such as snake species, age, seasonal period and diet [112]. There are 13 species of rattlesnakes in Arizona are most active from March through October and shelter in abandoned burrows of other animals, brush/ woodpiles, and rock crevices. They generally eat small mammals (rodents), lizards, and birds. Rattlesnakes use camouflage as a defense mechanism and to help them catch prey. While camouflage makes it difficult for people to see and avoid them, their audible rattle provides an exceptional warning most of the time [66]. *B. jararacussu*, *B. brazili* and *B. atrox* venoms at concentrations up to 5 mg/mL were able to induce

breakage in the DNA of human lymphocytes [113]. Hump-nosed pit vipers of genus *Hypnale* are the commonest cause of snake bite in Sri Lanka [114]. Metallo-and serine proteases have been identified in several colubrid venoms, and phospholipase A2 is a more frequent component than has been previously recognized. Venom phosphodiesterase, acetylcholinesterase and prothrombin activator activities occur in some venoms. Postsynaptic neurotoxins and myotoxins have been partially characterized for venoms from several species [115]. Moreover, the venom of the family Viperidae, including the saw-scaled viper, is rich in serine proteinases and metalloproteinases, which affect the nervous system, complementary system, blood coagulation, platelet aggregation and blood pressure [116]. Novel hyaluronidase CcHaseII (33 kDa) of the most dangerous Egyptian horned viper *Cerastes cerastes* (Cc) is purified. The spreading property of the purified enzyme promoted distribution of other venom components and generalized tissue destruction. The importance of venom hyaluronidase as a therapeutic target and identification of nontoxic inhibitors of the enzyme could play an important role in the efficient management of snakebite [117].

Myotoxins play a major role in the pathogenesis of the envenomations caused by snake bites in large parts of the world where this is a very relevant public health problem. They are basic proteins that can be classified into three main groups belonging to structurally distinct protein families: the 'small' myotoxins, the cardiotoxins and the PLA2 myotoxins [118]. The pathology caused by cardiotoxins and PLA2 myotoxins develops rapidly and it is associated with marked damage to the sarcolemma, whereas pathology associated with 'small' myotoxins has a more delayed onset and sarcolemma damage is not apparent [119]. Among fast acting myotoxins, cobra cardiotoxins, they cause severe tissue necrosis and systolic heart arrest in snakebite victims. Lys49-PLA2 myotoxins, an important component of various viperid snake venoms, they cause severe myonecrosis. So, these toxins are used as tools to study skeletal muscle repair and regeneration, a process that can be very limited after snakebites [120].

Snake venoms are a rich source of molecules act via the adhesion molecules. The benefits of these molecules for the treatment of certain diseases are: a shorter half-life, reversible inhibition, easier to control a problem and very low immunogenicity. For example, the antihypertensive drug captopril, modelled from the venom of the Brazilian arrowhead viper (*Bothrops jaracusa*); the anticoagulant Integrilin (eptifibatide), a heptapeptide derived from a protein found in the venom of the American southeastern pygmy rattlesnake (*Sistrurus miliarius barbouri*); Ancrod, a compound isolated from the venom of the Malaysian pit viper (*Agkistrodon rhodostoma*) for use in the treatment of heparin-induced thrombocytopenia and stroke and alfimeprase, a novel fibrinolytic metallo-proteinase for thrombolysis derived from venom of southern copperhead snake (*Agkistrodon contortrix contortrix*) (Table 3).

Table 3. Drugs derived from snake venom [121].

Name	Snake	Target and function of treatment
Capoten ® (Captropil)	*Bothrops jaracusa*	Angiotensin converted enzyme (ACE) inhibitor/ high blood pressure
Integrilin ® (Eptifibatide)	*Sisturus miliarus barbouri*	Platelet aggregation inhibitor/acute coronary syndrome
Aggrastat ® (tirofiban)	*Echis carinatus*	GPIIb-IIIa inhibitor/myocardial infarct, refractory ischemia
Exanta	*Cobra*	Thrombin inhibitor/arterial fibrillation and blood
Alfimeprase	*Agkistrodon contortrix contortrix*	Thrombolytic/ Acute ischemic stroke, acute peripheral arterial occlusion
Ancrod ® (viprinex)	*Agkistrodon rhodostoma*	Fibrinogen inhibitor/ stroke
hemocoagulase	*Bothrops atrox*	Thrombin-like effect and thromboplastin activity/ prevention and treatment of haemorrhage

The boldly colored *Gila monster* is a venomous reptile can deliver a painful bite if handled. *Gila monster* move slowly and feed on animals that cannot easily escape, such as young rodents and the eggs of other reptiles and ground-nesting birds. They are most active in the spring and take refuge underground during hot weather. Fortunately, *Gila monster* attempt to bite humans only as a defensive measure when they feel threatened and always prefer escape to defense. *Gila monster* is a venomous reptile found in the lower elevations of southern and western Arizona. They can deliver a painful bite if handled. *Gila monster* are most active in the spring and take refuge underground during hot weather [66]. Sea snakes are mainly a hazard to fishermen in the subtropics and tropics who are bitten when emptying fishing nets or when wading in muddy waters. Rhabdomyolysis is the main feature of envenomination by sea snakes. Early clinical signs are muscular pain and tenderness followed by placid paralysis and renal failure [2].

7d. Class Aves

Homobatrachotoxin was reported in 1992 to occur in the skins and feathers of three passerine bird species in the genus *Pitohui* (family Pachycephalidae) endemic to New Guinea and considered toxic by New Guineans [122].

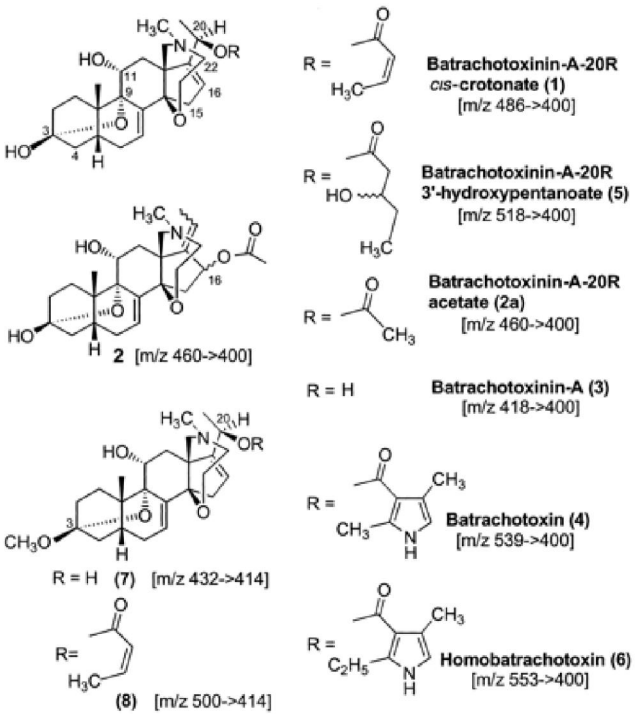

Fig. 1. Batrachotoxins found in feathers and/or skins of New Guinean passerine birds [124].

Homobatrachotoxin is a member of a group of neurotoxic steroidal alkaloids, collectively called batrachotoxins that stabilize the open form of voltage-gated sodium channels in nerve and muscle membranes [123]. Dumbacher et al. [124] were detected and measured batrachotoxins by using HPLC-mass spectrometry, in five species of New Guinean birds of the genus *Pitohui* as well as a species of a second toxic bird *Ifrita kowaldi*.

The alkaloids, identified in feathers and skin, were batrachotoxinin-A cis-crotonate (1), batrachotoxinin-A and an isomer (3 and 3a, respectively), batrachotoxin (4), batrachotoxinin-A 3′-hydroxypentanoate (5), homobatrachotoxin (6), and mono- and dihydroxylated derivatives of homobatrachotoxin. The highest levels of batrachotoxins were generally present in the contour feathers of belly, breast, or legs in *Pitohui dichrous*, *Pitohui kirhocephalus*, and *Ifrita kowaldi*. Lesser amounts are found in head, back, tail, and wing feathers. Batrachotoxin (4) and homobatrachotoxin (6) were found only in feathers and not in skin. The levels of batrachotoxins varied widely for different populations of Pitohui and Ifrita, a result compatible with the hypothesis that these birds are sequestering toxins from a dietary source (Fig. 1).

Feathers constitute the first line of defense against consumers in birds. Many predators such as raptors and carnivores, pluck them from carcasses before commencing to feed. Thus, it is not surprising from a functional standpoint that feathers serve as a repository of defensive chemicals. Dumbacher et al. [124] suggested that batrachotoxins might be transferred from feathers onto eggs or nest materials, thus affording protection against nest-raiding vertebrates. Breast or belly contour feathers contained the highest toxin concentrations and might rub off onto eggs or be deposited in the nest to provide protection from predators such as snakes, rodents or other birds; particularly any predator that might normally eat an egg whole.

Batrachotoxins found in *Pitohui* or *Ifrita* feathers may repel or kill lice or other parasites [125]. In addition, batrachotoxin-laden dander or feather pieces shed from the birds may impart these nonvolatile toxins to other organisms including humans. A survey of birds for batrachotoxins and related compounds also is illustrated, particularly in light of the discovery of alkaloids in the red warbler (*Ergaticus ruber*) from Mexico [126].

7e. Class Mammals

The occurrence of venom in mammals has long been considered of minor importance. Mammalian venoms form a heterogeneous group having different compositions and modes of action and are present in three classes of mammals, Insectivora, Monotremata, and Chiroptera. A fourth order, Primates, is proposed to have venomous representatives [127]. The taxonomically complex group Insectivora holds most of the venomous mammals. With the exception of vampire bats, these are the only mammals so far observed to produce toxic saliva. The American shorttailed shrew (*Blarina brevicauda*), the Hispaniolan solenodon (*Solenodon paradoxus*), the European water shrew (*Neomys fodiens*) and the Mediterranean water shrew (*Neomys anomalus*) provided the most definite evidences for salivary venom [128]. European folk-tales focused on the effects of shrew bites upon cattle and horses, describing the affected animals as paralyzed and deprived of feeling, hinting to systemic effects [129]. The purification of the toxic component of the *B. brevicauda* saliva, blarina toxin was achieved by Kita et al. [130] as a glycosylated protein composed of 253 amino acids with a kallikrein-like protease activity. This toxin cleaves kininogens producing kinins, including bradykinin, an inflammation mediator which increases vascular permeability and lowers blood pressure.

The platypus (*Ornithorhynchus anatinus*) is thought to be the only venomous Monotremata representative. When gland secretion of platypus was injected subcutaneously into a rabbit it produced localized swelling and tenderness. However, intravenously injection into a rabbits it caused a rapid fall in blood pressure and respiratory distress were observed, being followed by death [131]. The *O. anatinus* venom is a complex mixture of 19 different fractions. The peptide fractions include C-type natriuretic peptides, defensin-like peptides, nerve growth factors, isomerases, hyaluronidase, protease, and uncharacterized proteins [132, 133]. Two distinct classes of anticoagulants are found in the saliva of vampire bats i.e. plasminogen activators and inhibitors of proteinases [134]. Plasminogen activators act producing localized proteolysis in tissue remodeling, wound healing and neuronal plasticity [135]. The venom of a loris reaches the target animal by means of prolonged bites. It was originally thought that the animal's salivawas responsible for the observed symptoms, causing anaphylaxis on already sensitized individuals [136]. Alterman [137] established a connection between this habit and the painful loris bites, proposing that toxins from the brachial gland exudate would be responsible for the observable effects on humans. The brachial gland exudate is a complex mixture, comprising volatile low molecular weight metabolites and non-volatile high molecular weight protein fractions [138]. An unidentified steroid and polypeptides generated by mixing brachial gland exudate and saliva were suggested to be the active toxic component of the venom [139].

Table 4. Summary of venomous mammals and their venoms [127].

Mammalian Order	Venomous representatives	Venom source	Known toxic components	Most common effects
Insectivora	Shrews and solenodons	Salivary gland	Blarina toxin	Breathing disturbance, paralysis and convulsions
Monotremata	Platypus	Crural gland	C-type natrituretic peptides, defensin-like peptides, nerve growth factor	Acute pain and swelling
Chiroptera	Vampire bats	Salivary gland	Plasminogen activators, Draculin is a glycoprotein found in the saliva of vampire bats	Prolonged bleeding
Primates	Slow and pygmy slow lorises	Brachial gland	BGE protein (is a heterodimeric protein with 17.6 kDa)	Allergic reactions

CONCLUSION

Very many poisonous animals are medically important. Envenomation causes multiple disorders of which neurotoxicity is sometimes the major problem. Some of the natural toxins acting on the cardiovascular system are very potent and highly specific for some receptors in cardiac tissue. Although some molecules of venoms possess high receptors specificity, they are used as therapeutic drugs. More studies on their structure-function may provide useful information for synthesis of smaller analogues with lower toxicity. So, interventions by scientists and clinicians have made it possible to use the venom proteins as potential drugs for multiple disorders or for drug design.

TRANSPARENCY DECLARATION

The authors declare no conflicts of interest.

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