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Review Article

Effects and Medicinal Value of Animal Venoms/Toxins

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Abstract

During evolution, some creatures have been able to develop special organs for the production of various venoms and their injection into other creatures. Either for protection from predators or to attack and immobilize their prey. Animal venoms are extremely complex mixtures of various different proteins and peptides which produce diverse physiological effects and have a variety of molecular targets. Even minor changes in the amino acid sequence of the protein may give rise to new biological properties. Venoms may be of different types based on their effect on the body such as, neurotoxic (affects the central and peripheral nervous systems), hemotoxic (affects the bloodstream by acting on the cardiovascular system), proteolytic (damages tissue proteins causing necrosis) and cytotoxic (affects the area at the site of the injection). In spite of all their dangers, venoms have a great medicinal value apart from producing antivenoms. The enzymes and proteins found in the venom of most animals can be used to detect and cure diseases such as cancer, AIDS, Alzheimer's, diabetes etc. and many more are yet to be discovered. In this paper we will discuss the effects and medicinal value of a selective few creatures such as the waxy monkey tree frog (Phyllomedusa sauvagii), gila monster, and the pit viper (jararaca). Even though these venoms pose a threat to the lives of humans and other creatures it is worth keeping them around because the number of lives that they save transcend the lives they take.

Keywords: *Venom; Neurotoxic; Hemotoxic; Peptides; Necrosis; Diseases; Waxy Monkey Tree Frog; Pit Viper; Gila Monster*

Introduction

When an organism elicits a venom, its final form may consist of hundreds of varying bioactive chemicals that interact with each other producing its toxic effects in the body of the victim. This homogeneous mixture includes different types of proteins, peptides and non-peptidergic molecules [1]. Peptide toxins that are found in most venoms (cone snail, spider, scorpion, snake), act on ion channels and block them leading to an inhibition of neuronal signals. Neurotoxins found in most spiders and scorpions block voltage gated ion channels (depolarize when membrane potential reaches threshold), while neurotoxins found in snakes block ligand gated ion channels (depolarize when a particular ligand or protein binds to the receptor thus activating it) particularly nicotinic acetylcholine receptors. There are two broad classes of enzymes found in venoms namely, oxidases (catalyzes an oxidation-reduction reaction) and hydrolases (catalysts that use water to break chemical bonds) [2]. Until now, only a single oxidase, L-amino acid oxidase, has been found in venoms, whereas hydrolases are profuse and include phospholipases A2, acetylcholinesterases, peptidases and hyaluronidases [3]. Non-enzymatic proteins are more diversified in venoms. In snakes they include three finger toxins, disintegrins (platelet aggregation inhibitors), proteinase inhibitors (inhibition of enzymes that break down proteins), nerve growth factor etc. The active components of these venoms are isolated, sterilized and

screened in assays. These assays may be either phenotypic (to identify the compound that alter the phenotype of a cell or an organism in a desired manor) known as forward pharmacology, or target directed assays (to identify the biological target of the substance and understand its underlying mechanism of action) known as reverse pharmacology [4]. Using these methods, venoms provide a new perspective to basic research and contemporary ideas for the development of new therapeutic drugs.

Waxy monkey tree frog (*Phyllomedusa sauvagii*)

The waxy monkey tree frog or *Phyllomedusa sauvagii* has developed a physiological adaptation to protect itself from pathogens and limit water loss through its skin by toxic secretions of a complex mixture of bioactive peptides and alkaloids. Most of these alkaloids and toxins are harvested from their insect diets. The peptides and alkaloids found in the venom of the frog can be used to treat a wide range of diseases including [6]. Some of depression, cancer, AIDS, Alzheimer's and Parkinson's and even to reduce pain these peptides include dermaseptin, phyllokinin, sauvagine, caerulin, epibatidine and dermorphin. In the course of this review we will only be covering a few of them [7].

Figure 1

Dermaseptins

Dermaseptins are a group of peptides, found in the skin secretions of the *Phyllomedusa sauvagii*. They belong to a larger family of cationic membrane disruptive antimicrobial peptides which exhibit a wide array of antibacterial (against pathogenic microorganisms), tumoricidal (agent destructive to tumors), and antiproliferative activities (inhibits or prevents the spread of cancer cells) depending on a coil to helix transformation [8].

Due to their cationic charge (+), it readily combines with the anionic membranes (-), thus penetrating through and causing disruption of microorganisms. This action of dermaseptins makes them responsible for their antimicrobial/antibacterial efficiency [9]. The Val-Gly pairing present in dermaseptins, divides the peptide into two segments to form a helix-hinge-helix structure which facilitates the formation of hydrophobic residues on both extremities to insert into the membrane and instigate permeability in most microorganisms [10]. Once the accumulation of peptides on the membrane of the microorganism reaches its threshold, the composite of cationic peptides and the anionic lipids form a positive curvature of the bilayer and then its permeation or disruption occurs (according to the carpet mechanism) [11].

Dermaseptin-PS4 (Der-PS4), and dermaseptins B2 and B1 also displayed antiproliferative activity against five tested cancer cell lines but exhibited slight cytotoxicity on normal human cells. However, its exact underlying mechanism of action is not well understood yet. The most recent and dominant perception is that the electrostatic interactivity between the cationic antimicrobial peptides and anionic cancer cell membrane is one of the main expositions for the effect [12]. After the accumulation of peptides on the tumor cell membrane, by electrostatic interaction, the cationic peptides (destructured in an aqueous media) adopt an a-helical structure, penetrate through the cell membrane and evoke the disruption of the membrane followed by necrosis via cell lysis (disintegration) and eventually cause the death of the cancer cell. The negatively charged molecules situated on the cancer cell membrane e.g. glycosaminoglycans, O-glycosylated mucins and phosphatidylserine play a vital role for the interaction between the membrane and anti-tumor peptides. It was also deduced that the antiproliferative mechanisms of Der-PS4 are the combined effect of electrostatic interplay along with other antineoplastic pathways depending on its concentration.

In the current day situation, with bacteria constantly adapting and increasing resistance towards conventional antibiotics the demand for novel antibacterial pharmaceuticals are rising. Therefore, it is essential to understand the underlying mechanisms of dermaseptins against different pathogens in order to tailor them into a molecule which can target specific clinical problems such as cancers, and diseases caused by certain microorganisms.

Epibatidine

One of the alkaloids found in the waxy monkey tree frog, epibatidine displayed analgesic effects which turned out to be 200 times more potent than the opioid morphine and had 30 times the potency of nicotine [13]. The analgesic effect that this toxin exerts is attributed via its interaction with nicotinic acetylcholine receptors (nAChR) more specifically to the a4/b2 and a3/b4 subtypes which are transmembrane oligomeric ligand gated ion channels that are expressed both centrally and peripherally at the postsynaptic membrane of neurons. When the neurotransmitters bind to these receptors it results in the opening of ion channels, allowing the entry of sodium and calcium ions into the membrane. This causes depolarization in the postsynaptic membrane inducing an action potential that propagates the signal further. This signal ultimately induces the release of dopamine and norepinephrine, leading to an antinociceptive effect on the organism [14]. The interest in epibatidine arises from the discovery that its analgesic activity is mediated by non-opioid receptors which obliterates the risk of dependence on the drug or addiction. But since epibatidine binds to nAChRs in the central nervous system as well as in the skeletal neuromuscular junction, it activates exocrine glands, causing seizures, and muscle paralysis. The paralytic effects of epibatidine is due to its ability to bind to muscle type nicotinic receptors [15].

The central receptors are involved in various neurological conditions including schizophrenia, Parkinson's disease, Alzheimer's disease and even in other cardinal functions such as neuroprotection, memory, learning and pain control [16]. Sometimes epibatidine might bind to muscarinic acetylcholine receptors causing hypertension, bradycardia and muscular paresis, resulting in a limited therapeutic index [17].

Therefore researchers have switched to modifying the epibatidine structure to acquire analogues with an improvised pharmacological activity to toxicity ratio and a selectivity for different nAChR subtypes. Eg: ABT-594 also known as tebanicline was a compound developed from epibatidine to treat neuropathic pain and did not induce any sedative-like side effects [18]. ABT-418, another derivative of epibatidine is used in the treatment of cognitive dysfunction and less severe attention deficit hyperactivity disorder (ADHD) in adult patients who now tolerate its minor side effects including nausea, headaches and dizziness. Thus, the pharmacological effects of epibatidine reveal newer perspectives to drug therapies and serve as a predominant research instrument to analyze the activity of nAChR.

Sauvagine

Sauvagine is a potent and broad spectrum biologically active polypeptide of 40 amino acid residues originally obtained from the skin secretions of the *Phyllomedusa sauvagii*. Its structure is similar to the peptide, corticotropin-releasing factor (CRF) found in the mamma-

lian brain [19]. The CRF family of signalling molecules including sauvagine is involved in regulating centrally-mediated responses to stress by activating the adrenocorticotropic hormone (ACTH) which in turn causes the secretion of cortisone (stress hormone). It even plays an important role in adjustments of the cardiovascular, reproductive, digestive, and immune systems to various kinds of challenges. They exert their biological activities by binding to the G protein-coupled receptors (GPCRs) that are positively coupled to adenylate cyclase (CRF1 and CRF2 receptors), thus activating a second messenger system which brings about further changes [20].

The *Phyllomedusa sauvagii* sauvagine (PS-Svg) radioligands have been the standard for audiographic localisation of CRF receptors in a variety of species. The PS-Svg radioligands bind to major sites of cellular CRF1 receptors in the brain, such as the isocortex, hippocampus, and the cerebellum, and to areas with profuse CRF2 receptors, such as the nucleus of solitary tract, lateral septum, and the choroid plexus [21]. Sauvagine is used in the pharmaceutical industry as diuretics (increases urine production via cyclic AMP dependent second messenger mechanisms) and may be used to treat cardiovascular and endocrine system dysfunctions or irregularities along with other CRF-mediated disorders.

Dermatoxin and phylloxin

Dermatoxin and phylloxin are antimicrobial peptides derived from their precursor, a complementary DNA (cDNA) cloned from a lyophilized skin secretion of the *Phyllomedusa sauvagii*. It has now been discovered that they are involved in the process of angiogenesis (formation of new blood vessels) by its interaction with the Vascular Endothelial Growth Factor (VEGF) receptors [22]. The VEGF ligand is essential to the angiogenesis process during the development of cancerous tumors. The VEGF ligand complex is activated by the upstream activators. This includes growth factors and oncogenes (genes with the potential to cause cancer). As a result VEGF binds to its receptors on the surface of the endothelial cells which in turn activates the intracellular tyrosine kinase. This induces a downstream signalling cascade that triggers angiogenesis. Angiogenesis is primarily mediated through the interaction of VEGF-A with VEGF receptor -2 whereas the other variants of the VEGF ligand and receptor play a secondary role in this process [23]. Phylloxin and dermatoxin, tend to switch off the process of angiogenesis, thus starving the cancerous tumor cells from growing. These peptides act as VEGF inhibitors or competitive antagonists which inhibit the VEGF signalling process by binding to the VEGF receptors (VEGFR-1 and VEGFR-2). This would encourage the tumor cells not to spread and in more likely situations end up killing the cancer cells which is significant in regards to the pharmaceutical applications incorporating this amphibian's peptides.

Pit Viper (*Bothrops jararaca*)

Snakes can be extremely dangerous and represent a threat to lives, whereas on the other hand, components of various snake venoms act as beneficial tools for treatments of numerous human diseases. Snake venoms are a cocktail of secretions including toxic and biologically active proteins and peptides, produced and injected by a pair of specialized exocrine venom glands connected to the fangs via ducts. Some other components present in snake venoms include nucleosides, carbohydrates, amino acids, lipids and metallic cations like sodium, zinc (for activation of anticholinesterase which is an acetylcholinesterase inhibitor), calcium (for phospholipase activity) and cadmium (to inhibit biological processes in specific enzymatic activities) [24]. The inherent stability of the peptides in snake venom helps them reach their target receptors inside their prey. Not only can snake venoms help treat certain diseases, but they have also proved to be invaluable tools in determining the structure and functions of various receptors [25]. Viper venom is typically haemotoxic (blood toxins), necrotising (tissue death) and anticoagulant (preventing blood from clotting) [26].

In this review we will examine some of the components from the venom of the Brazillian Pit Viper or the *Bothrops jararaca*, which can be used in the pharmaceutical industry such as phospholipase A2, bradykinin potentiating peptides and the three-finger toxins.

Figure 2

Phospholipase A2 (PLA2)

Isolated from the venom of the *Bothrops jararaca*, PLA2 displayed myotoxicity, neurotoxicity, proinflammatory, hemolytic, anticoagulant, antibiotic effects and even anti-plasmodium activities [27]. During envenomations, they induce the digestion of the prey. Phospholipase A2 (PLA2) catalyzes the hydrolysis of fatty acids at the sn-2 position of the phospholipid membranes, and releases lysophospholipids and free fatty acids, especially polyunsaturated ones like arachidonic acid. Considering the fact that PLA2s from snake venoms are able to act directly on phospholipid membranes, they should be able to promote alterations in lipid biosynthesis and dysregulation of lipogenesis that could have a huge impact on the metabolic rate of tumor cells and also on the formation of lipid mediators derived from arachidonic acid (performs important roles in inflammation) [28]. Hence PLA2 might serve its usefulness as a tool to closely examine the mechanisms involved in cancer and inflammation [29], and maybe even act as molecular models for new antitumor and anti-inflammatory drugs [30]. Another feature of PLA2 is its ability to inhibit adenosine diphosphate (ADP) -induced platelet aggregation causing hemorrhages or internal bleeding. On the other hand they can also be used as blood thinners or anticoagulants in cases of blood coagulation [30]. Various PLA2 regulatory and activation mechanisms are credited to different receptor ligand interactions. For instance, bacterial endotoxins stimulate increased biosynthesis of cytosolic PLA2 proteins via a pathway involving mitogen activated protein kinase (MAPK) and Platelet Activating Factor (PAF) acts via a 7-transmembrane receptor to stimulate increased secretory PLA2 proteins. These varied PLA2 activating pathways are promising targets for pharmaceutical modulation of PLA2 actions in pathophysiology [32]. A PLA2 inhibitor was also isolated from the *Bothrops jararaca* known as yBjPLl. The inhibitory activity of enzymatic, edema and myonecrotic activities by yBjPLl suggests its role for protection of the snake against its own venom. PLA2 has even been found to express antitumor and antimicrobial activities. Other peptides found in the venom of the *Bothrops jararaca* with similar effects as PLA2s include Metalloendopeptidase, C-type lectin and Disintegrin.

Bradykinin-potentiating peptides (BPPs)- Bj-BPPs

Bradykinin-potentiating peptides (BPPs) exert their effects by inhibiting the angiotensin-converting enzyme (ACE) and are associated with antihypertensive and vasodilator activities [33]. In the case of BPPs or proline-rich oligopeptides (PROs) isolated from the venom of the *Bothrops jararaca*, BPP 5a (Bj-PRO-5a) induces hypotension via muscarinic and bradykinin receptors [34]. It was recently discovered that Bj-BPPs promoting vasodilation wasn't only due to a decrease in angiotensin II formation or to the increase of bradykinin

concentration, but it also involved the production of nitric oxide (NO). NO diffuses through smooth muscles, where it activates guanylate cyclase which converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). This further promotes relaxation of blood vessels [35]. In endothelial, NO originates from L-arginine (protein builder in the body) by the action of endothelial NO synthase (eNOS), whose activity increases with an increase in cytosolic calcium levels (Ca^{2+}) by receptor activity. Both bradykinin (BK) B2 receptors and muscarinic acetylcholine receptors (mAChRs) have the ability to induce Ca^{2+} ion transients that result in eNOS activation and NO production for promotion of vasodilation [36]. Nitric oxide is a key mediator for the maintenance of functionality and integrity of the endothelium including the regulation of the vascular tonus (degree of constriction of a blood vessel), prevention of leukocyte filtration, angiogenesis and thrombus formation [37]. However, the Bj-PRO-5a mechanism of action may not involve a direct action on BK B2 receptors or BK accumulation but potentiates BK-induced effects. The structure of BPPs like that of the *Bothrops jararaca* is used as a scaffold for the development of the anti-hypertensive drug - Captopril. Due to its ability to dilate blood vessels it is used in creams for muscle pain relief. Other therapeutic applications of Bj-PRO-5a in the future are not only limited to the treatment of cardiovascular diseases. Researchers are working on mAchR-M1 receptor agonists for the treatment of cognitive disorders such as Alzheimer's disease (linked to mAchR-M1 degradation) [38]. Furthermore this peptide could be used as a tool to examine cross-talk mechanisms between the two Gq-protein coupled metabotropic receptors. Another peptide similar to the Bj-PRO-5a found in the venom of the *Bothrops jararaca* are the C-type-natriuretic peptides.

Three-finger toxins (3FTX)

Three-Finger Toxins (3FTX) are mini proteins that are usually found in the venom of members of the Elapidae family. However, to a smaller extent they were recently discovered in the venom of the *Bothrops jararaca* (Viperidae family) [39]. Thus, the possibility arises that the 3FTXs may be responsible for the ability of the venom of the jararaca to treat CNS related disorders. A distinct structural feature of the 3FTX is its unique fold consisting of three loops (beta stranded), emerging from a hydrophobic spherical core. Subtle variations in the length of their loops, amino acid residues and conformations are responsible for their distinct biological activities [40]. They act on a vast variety of targets including nicotinic receptors, muscarinic receptors, acetylcholinesterase, adrenergic receptors, calcium channels and potassium channel-interacting proteins. The number and diversity of channels receptors and enzymes identified as targets is increasing continuously. Such a diversity highlights its adaptability for generating pleiotropic functions (producing multiple effects on a single gene). Although the 3FTXs affect many biological systems due to their interaction with an array of molecular targets, their most significant target is the cholinergic system. By blocking the activity of the nicotinic and muscarinic acetylcholine receptors or by inhibiting the release of the enzyme acetylcholinesterase, 3FTX drastically interferes with the proper functioning of the neuromuscular junction. 3FTX cardiotoxins are under scientific investigation for cancer inhibitory studies and its potential use as an antimicrobial agent because of their ability to cause lysis in various types of cells with low cytotoxicity [41]. These toxins have become powerful pharmacological tools for studying the function and structure of their wide range of molecular targets. Since the dysfunction of these receptors and enzymes are involved in many diseases, the 3FTX could be used to create highly specific therapeutic agents for those diseases [42].

Gila monster (*Heloderma suspectum*)

The Gila monster is a species of venomous lizard native to the southwestern United States. It's a heavy and typically slow moving lizard up to 60cm in length. It produces venom in modified salivary glands in its lower jaw. Since it lacks the musculature to inject the venom it is propelled from the gland to the tooth by chewing. By capillary action the venom is brought out of the tooth and into the victim. Due to its sluggish movement the Gila monster isn't considered a threat to human lives [43]. However, its venom is about as toxic as that of a diamondback rattlesnake and if bitten, the victim may experience excruciating pain, edema, nausea and weakness associated with a rapid drop in blood pressure. A few potentially lethal toxins have been isolated from the venom of the Gila monster, which cause hemorrhage in internal organs, exophthalmos (bulging of the eyes), lethargy and partial paralysis of the limbs. Although its venom is so dangerously toxic, it has its fair share of uses in the pharmaceutical industry. A few bioactive peptides and other components isolated from the venom

of the Gila monster are an active area of research promising new treatments for diseases like Alzheimer's [44] and diabetes and even cancer [45].

Figure 3

Exendin-4

The component of the Gila monster's venom of greatest scientific interest is a peptide known as exendin-4. In 1990 a research was conducted by endocrinologist Dr. John Eng which showed that the venom from certain snakes and lizards including the Gila monster caused enlargement of the pancreas. That research suggested that the compounds present in the venom of those creatures were somehow overstimulating the pancreas [46]. He further assayed the venom and discovered a peptide he named exendin that triggers synthesis and release of insulin from beta cells in the pancreas. He also discovered that exendin-4 was similar in structure and function to Glucagon Like Peptide-1 (GLP-1), a hormone found in the human body pancreas that stimulates insulin production, but only when glucose production is high. Like GLP-1, Exendin-4 is a GLP-1 receptor agonist. It interacts with GLP-1 receptors (binds directly to the N-terminal domain of the receptor), which are G-protein coupled receptors, in the body inducing cyclic adenosine monophosphate (cAMP) release adenylyl cyclase second messenger pathways, including protein kinase A and Epac, just like GLP-1 [47]. The activation of GLP-1 receptor triggers Ca^{2+} induced exocytosis of insulin-containing vesicles to facilitate insulin secretion. Immediately after a meal GLP-1 remains active in the body for about 2 minutes whereas exendin-4 remains active for hours indicating its long lasting effect for the treatment of diabetes [48]. This is because exendin-4 is more stable against enzymatic degradation by dipeptidyl-peptidase (DDP-4) as compared to endogenous GLP-1. Exendin-4 exhibits a 400 times higher binding affinity than the GLP-1 peptide towards an isolated N-Terminal Domain (NTD) preparation of the receptor. It shows 53% similarity with the human GLP-1 peptide in addition to a 9 residue C-terminal extension which is absent in the GLP-1. Exendin-4 retains its string helicity at its N-terminal due to the presence of helix favouring glutamate residue which is not found in the GLP-1 peptide. Diabetic nephropathy and neuropathy are both critical disorders seen in diabetic patients. Exendin-4 prevents diabetic neuropathy with pronounced neuroprotective effects [49]. These effects of exendin-4 are linked to its anti-apoptotic actions and restoration of cAMP levels [50]. Exendin-4 also prevents the impairment of cognitive functions in type 2 diabetes mellitus via modulation of inflammation, attenuation of oxidative stress and maintenance of normal synaptic function [51]. Other than its therapeutic properties for diabetic complications, exendin-4 displayed wound healing properties attributed to its anti-inflammatory activities and promotion

of angiogenesis. In a recent study exendin-4 was found to elevate the level of tyrosine hydroxylase (a key enzyme for the formation of L-Dopa, which is the rate-limiting biosynthesis step of dopamine) in the substantia nigra and striatum. It has been proved as a useful and effective therapeutic option for Parkinson's and Alzheimer's disease. Clinical trials for exendin-4 in these 2 diseases are in progress.

Helodermin

Helodermin is a peptide isolated from the salivary venom of the lizard *Heloderma suspectum* [52]. They have been compared to vasoactive intestinal peptide (VIP) with respect to its effect on systemic blood pressure by relaxing smooth muscles. They reduce blood pressure in a dose-dependent manner. Helodermin activates adenylate cyclase which promotes the second messenger system in membranes of the human heart by the generation of cyclic adenosine monophosphate (cyclic AMP) out of ATP, showing properties that are analogous yet distinct from those of VIP and other such peptides. Cyclic AMP modifies cell function in virtually all eukaryotic cells via the activation of cyclic AMP-dependent protein kinase or through cyclic AMP- gated ion channels [53]. Therefore, helodermin extracted from the venom of the Gila Monster is used in antihypertensive medications by assisting vasodilation and hypotension [54]. Helodermin is also being researched for their use in drugs for the treatment of cancer [55].

Concluding Remarks

Venoms of various animals can sometimes prove to be life threatening, but they usually save more lives than they take. They are also extremely beneficial in pharmacological research and analysis such as in the investigation of ion channel functions by examining how the peptides bind to their respective receptors and the effects that they have on the ion channel. Furthermore, synthetic methods such as cyclization, minimization, and the usage of diselenide bridges may help us overcome the challenges that have to be faced between the initial discovery of the toxins and their clinical application which would enable their use as therapeutic drugs. Everyday a new toxin or peptide is discovered from some creature, which leads to another solution and cure for a disease and helps us understand the underlying mechanisms of our own bodies in much greater depth.

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