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A review on spider toxins a useful source of pharmacological peptides

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ABSTRACT

Spider venoms are complex mixtures or cocktails of toxic proteins and peptides that have been evolved during very long evolution. It is used by spiders for prey capture and/or defense. Spider venom shows variable pharmacological activity and affect various cell targets due to presence of diverse lethal and toxic peptides. It activate excitatory ion channels present on somatosensory neurons and produce a noxious sensation in mammals. Spider toxins cause reversible blockage of cation selective quisqualic acid sensitive glutamate receptor in insects and inhibit associated ion channels in the vertebrate central nervous system. Spider toxins inhibit voltage-activated potassium channels by binding to a critical helix-turn-helix motif and partition into membranes to bind the paddle motif and alter the structure and function of different types of ion channels. Besides this, spider toxins show multiple local and systemic effects like severe pain, inflammation, neural, renal and cardiac toxicity. Due to their selective binding to ion channels toxin peptides can be used as potent molecular probes to determine structure and function of ion channels. Further, studies on toxin-receptor interactions can be used for drug development mainly peptide therapeutics. In present review article pharmacological effects of various spider toxins and their mechanisms of action are explained in detail.

Key words: Spider venom, toxin, ion channel blockers, neurotoxin, latrotoxin, acid-sensing ion channels

INTRODUCTION

Venomous animals show a great diversity of toxins with multiple targets and clinical effects (Upadhyay and Ahmad, 2010). These animals show worldwide distribution with thousands of species in different regions. Spiders in tropical regions are particularly poisonous and dangerous to humans. Nearly 20,000 spider species are known, and almost all are venomous, although only 60 species worldwide are accounted poisonous to humans. Spiders exist in every place and ecosystem. Spider bite is benign and requires no intervention. Venomous spiders are the most medically significant group globally that causes significant physiological alterations in man and some times cause long-term disability in patients. In lower mammals spider venom causes significant morbidity and even deaths with a wide range of symptoms. Spider venom contains unique molecular diversity of venom components including substances of variable structure from simple low molecular weight peptides to large multi-domain proteins with different biochemical functions (Vassilevski *et al.*, 2009). It causes severe local and systemic reactions that may also occur sometimes in the pediatric population, resulting in admission to the pediatric intensive care unit. For such patients antivenin is highly required (Akyildiz *et al.*, 2009). Molecules accounting for lethal effects of venoms are mainly toxin peptides. Most of them have been isolated and extensively characterized for their biological activities. During long evolution, spider venom composition underwent continuous improvements, modifications, and adjustments for an efficient attack on predators and paralyzing of prey and/or as a repellent against aggressors (Jan *et al.*, 2006). Different venom components show synergistic action, thus providing efficiency of action of the mixture. Before making an attack spiders carefully learned to calculate accurately its dosage depending on the victim's size and resistance to the venom. If the amount of venom necessary for a particular hunted object exceeds its reserve, the spider wisely recedes or gives up stinging (Phillips *et al.*, 2005). Spider toxins show selective targets and bind to membrane ion channels that underlie ligand binding, gating, or ion permeation. Spider toxins can be served as invaluable tools for probing structure and function of various gated channels.

BIODIVERSITY OF SPIDERS

Most abundant toxin bearing species of spider are *Atrax robustus* (d-Atracotoxins), *Atrax versutus* (Versutoxin), *Hololena curta* (Curatotoxin), *Hysterocrates gigas* (Grammotoxin), *Phoneutria nigriventer* (Phoneutriatoxin), *Latrodectus mactans* (α-Latrotoxin), *Plectreurys tristis* (Plectoxin), *Agelenopsis aperta* (ω-Agatoxin), *Aptostichus schlingeri* (Aptotoxin), *Argiope lobata* (Agrotoxin), *Paracoelotes luctuosus* (δ-Palutoxin), *Selenocosmia huwena* (Huwentoxin-III), *Selenocosmia hainana* (Hainantoxin-VI), *Thrixopelma pruriens* (Protoxin-I) and *Haplopelma hainanum* (Hainantoxin-VI). Most of all toxins produced by these spiders are highly paralytic (Nicholson, 2007) (Table 1). The tarantula *Haplopelma hainanum* (*Ornithoctonus hainana*) occurs widely in the hilly areas of Hainan province in southern China. It is a highly venomous spider whose venom contains a variety of toxic components with different pharmacological properties. Different spider species possess pharmacologically different types of venom toxins with diverse function and structural composition (Fig. 1). These venom components show variable pharmacological activity and affect various cell targets. Spider venom activates excitatory channels present on somato-sensory neurons and produce a noxious sensation in mammals (Jan *et al.*, 2006). These generate paralysis, severe pain and even death.

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Table 1. Physiological effect of toxins isolated from different spider species

Common name	Scientific name	Toxin isolated	Physiological effects
Funnel web spider	*Atrax robustus*	δ-Atracotoxins	Block voltage gated Na+ channels
Funnel web spider	*Atrax versutus*	Versutoxin	Block voltage gated sodium channels
Funnel web spider	*Hololena curta*	Curatotoxin	Block neuromuscular transmission
Tarantula spider	*Hysterocrates gigas*	Grammotoxin	Block K^+ channel
Brazilian spider	*Phoneutria nigriventer*	Phoneutriatoxin	Block both Na^+ and K^+ channels and cause neuromuscular paralysis
Black widow spider	*Latrodectus mactans*	α-Latrotoxin	Act selectively on presynaptic nerve endings and cause massive release of neurotransmitters
Hunting spider	*Plectreurys tristis*	Plectoxin	Neuromuscular paralysis
Funnel web spider	*Agelenopsis aperta*	ω-Agatoxin	Act both pre- and post synaptically and cause neuromuscular block
		μ-Agatotoxin	Massive release of neurotransmitter and irreversible paralysis
Trap door spider	*Aptostichus schlingeri*	Aptotoxin	Neuromuscular block
Yellow sac spider	*Cheiracanthium punctorium*	CpTx 1	Cytotoxic and membrane damage activities
Orb-weaving spider	*Argiope lobata*	Agrotoxin	Inhibit glutamate receptors and associated ion channel in vertebrate central nervous system
Chinese spider	*Paracoelotes luctuosus*	δ-Palutoxin	Block voltage gated Na+ channels
Chinese spider	*Selenocosmia huwena*	Huwentoxin-III	Block neuromuscular transmission
Chinese spider	*Selenocosmia hainana*	Hainantoxin-VI	Neuromuscular paralysis
Peruvian greenspider	*Thrixopelma pruriens*	Protoxin-I	Block voltage gated Ca++ channels
Chinese bird spider	*Haplopelma hainanum*	Hainantoxin-VI	Neuromuscular paralysis

COMPOSITION

Spider venom is a complex multi-component mixture of biologically active substances (Wullschleger *et al.*, 2004). It is a pharmacopeia of toxin peptides (Shliapnikov *et al.*, 2010) with diverse biological activities (Veiga *et al.*, 2001) which are highly species-specific and depends on many factors including sex, nutrition, natural habitat and climate (Ferrat *et al.*, 2005). Spider toxins consist of basic peptides of 32-76 amino acids, but only exception is latrotoxin, which possess 1401 amino acids. Among spiders, two large venom groups are distinguished due to their mechanism of action i.e. neurotoxic and necrotic (cytolytic), although these effects can be exhibited simultaneously (Upadhyay, 2008). Spider venom also contains acylpolyamines (Yakehiro *et al.*, 2001) and polypeptides (Skinner *et al.*, 1989) which are proved highly lethal to smaller mammals (Nicholson *et al.*, 2004). Venom of the yellow sac spider *Cheiracanthium punctorium* (Miturgidae) contains CpTx 1 (15.1 kDa) as principal toxic component having 134 amino acid 134 residues. It represents a novel class of spider toxin with modular architecture and consists of two different yet homologous domains (modules) each containing a putative inhibitor cystine knot motif that shows potent insecticidal (paralytic and lethal), cytotoxic, and membrane-damaging activities. It causes stable and irreversible depolarization of muscle in both fly and frog neuromuscular preparations. This effect occurs receptor-independent and is inhibited by high concentrations of divalent cations (Vassilevski *et al.*, 2010). Spider venom toxins have high cysteine ratio, which are conserved at identical sequence position among toxin peptides and form four intra-molecular disulphide bridges (Fig. 1).

The venom toxin sphingomyelinase D (SMase D) isolated from sicariid spider venom (Loxosceles and Sicarius) causes dermonecrotic lesions in mammals. Multiple forms of venom-expressed genes with homology to SMase D are expressed in venoms of both genera. SMase D activity levels differ among major clades with American Sicarius vastly reduced relative to all Loxosceles and African Sicarius despite expression of SMase D homologs in venoms of American Sicarius (Zobel-Thropp *et al.*, 2010). Brown spider dermonecrotic toxins (phospholipases-D) are the most well-characterized biochemical constituents of *Loxosceles* spp. venom. It causes cutaneous and systemic effects such as dermonecrotic lesions, hematological disor-

ders, and renal. Further, new isoforms of toxins were generated by site-directed mutagenesis, which have shown phospholipase-D activity. The mutated toxin contains an alanine substitution for a histidine residue at position 12 in the conserved catalytic domain of *Loxosceles intermedia* Recombinant Dermonecrotic Toxin - LiRecDT1. It has helped to abolished dermatonecrosis mutation in rabbit skin and causes a significant decreased in inflammatory response. It show phospholipase-D dependent mechanism of toxicity, which has no substrate specificity and thus utilizes a broad range of bioactive lipids (Chaim *et al.,* 2011; Kapoor, 2010).

PHARMACOLOGICAL EFFECTS

Action on membrane bound receptors

Spider venoms are sources of highly specific substances affecting different systems of membrane transport such as ion channels, ionotropic receptors, etc. These substances are indispensable instruments or biological tool that can be used to study the membrane systems. These act as specific modulators in membrane transport system and can be in treatment of diseases associated with compromised membrane transport system functions (Michaelis, *et al.,* 1984). However, agatoxin isolated from *Agelenopsis aperta* has shown two classes i.e. beta/delta-agatoxin type that consist of 36-38 amino acid residues and originate from the venom of the agelenid funnel-web spider *Agelena orientalis.* It shows considerable amino acid sequence similarity to other known toxins such as μ-agatoxins, curtatoxins, and delta-palutoxins-IT from the related spiders *Agelenopsis aperta, Hololena curta,* and *Paracoelotes luctuosus.* beta/delta-Agatoxins modulate the insect Na(V) channel (DmNa(V)1/tipE) (Billen *et al.,* 2010). Besides this, toxins cause scratching, lacrymation, hypertension, sweating and agitation followed by spastic paralysis of the anterior and posterior extremities. One class, alpha-agatoxin consists of acylpolyamine toxins, which cause immediate but reversible paralysis in insects. These toxins also associate with glutamate sensitive receptor channels and block them (Branton *et al.,* 1987). The second class, μ-agatoxin includes six highly conserved disulphide bridge peptides, which cause irreversible paralysis in lepidopteran insects and flies. These toxins cause repetitive firing and massive transmitter release from postsynaptic stores at neuromuscular junction (Branton *et al.,*1987). Morespecifically, *A. aperta* venom acts on both pre and post synaptic junctions and show synergism in neuromuscular blockage. These different biochemical activities may also extend the venom's biological spectrum of activity to a wider range of insect prey (Skinner *et al.,* 1989).

Similarly orb weaver spiders contains a polyamine toxin that acts upon ionotropic glutamate receptors in the brain and causes acute generalized exanthematous pustulosis (AGEP) associated with viral infection, food allergens or toxins Venomous animals produce small protein toxins that inhibit ion channels with high affinity. These inhibitory proteins are water-soluble and bind at channel's aqueous-exposed extracellular surface (Lee and MacKinnon, 2004). Similarly ω-conotoxin binds by a non-competitive allosteric mechanism with rat brain synaptic plasma membrane vesicles (Nunes *et al.,* 1993). These toxin peptides do not affect transmission of glutamate receptors in the avian cochlear nucleus (Jackson *et al.,* 1987).

Disruption of calcium channels

Spider toxin causes pre synaptic disruption of calcium channels in *Drosophila* (Branton *et al.,* 1987) and mammals (Leung *et al.,* 1989). Acylpolyamines have shown insecticidal and fungicidal activity (Nicholson, 2007). Orb weavers spider causes paralysis, while curtatoxin from *Hololena curta,* spider and clubionid spider *Chiracanthium inclusum* induce a potent pre and post synaptic irreversibly blockage (Jackson *et al.,* 1987). α-Latrotoxin isolated form black widow spider *Latrodectus mactans tredecinguttatus* is a neurotoxin, it selectively acts on presynaptic nerve endings and stimulate secretion of neuromediators in vertebrates. This interaction of neurotoxins with the presynaptic receptor leads to the increase of the calcium ion concentration inside the cell, which stimulates hydrolysis of phosphoinositides (Scheer *et al.,* 1985). Besides this, it also enhance cation conductivity of bi-lipid layer due to the formation of cation selective ion channels (Branton *et a*l., 1987).

Similarly Brazilian "armed" spider *Phoneutria nigriventer* venom contains potent neurotoxins that show excitatory symptoms such as salivation, lachrymation, priapism, convulsions, flaccid and spastic paralysis. These neurotoxins emphasized pharmacological effects on ion channels and inactivate Na+ channels, blockage of K+ channels and do block calcium channels. Similarly, *Phoneutria keyserlingi* venom contains a series of polypeptides that are very similar. But, it shows difference to the venom of *P. nigriventer* in terms of their amino acid sequences and biological activities. Moreover, toxins from both *P. nigriventer* and *P. keyserlingi* evoke glutamate release and cause significant decrease in Ca2+ ions in synaptosomes of rat brain. Toxins from of both the species showed great similarity in the location of cysteine residues. However, species specific structural difference in amino acid sequences in spider toxins, lead to the significant changes in the pharmacological properties (Carneiro *et al.,* 2010).

Dermonecrosis, inflammation and hemolysis

Similarly, components of spider venom possess remarkable biological properties associated with their ability to act upon different molecules and receptors. The venom of Loxosceles spiders produces severe dermonecrotic damage, intravascular hemolysis, local inflammatory reaction, systemic alterations and edema. It contains *Clostridium perfringens* as microbial flora of in its venom glands. It inoculates this bacterium after bite and infects the wound site to exacerbate the dermonecrotic damage (Catalán *et al*., 2010). Similarly, *Loxosceles intermedia* causespublic health problem in the South Brazil having a rich source of novel compounds with diverse potential (Gremski *et al.,* 2010). Normally a painless bite of adult female *Loxosceles anomala* causes mild itching, followed by local, indurated swelling and a transient, generalized erythrodermic rash (Bucaretchi *et al.,* 2010). Toxins do leukocyte infiltration, release inflammatory mediators and stimulate the release of IL-6, MCP-1 and KC factors after envenomation. Similarly *L. gaucho* venom evokes an early complex inflammatory reaction, stimulating the secretion of pro-inflammatory cytokines and lipid mediators and recruiting leukocytes to the footpad (Barbaro *et al.,* 2010). Similarly, toxins isolated form Chilean black widow spider (*Latrodectus mactans*) increased the $Ca^{(++)}$ influx and trigger the acrosome reaction (Navarrete *et al.,* 2010).

Similarly *Phoneutria* (Ctenidae) is among the most dangerous venomous spiders found in Brazil. Its venom is composed of a mixture of pharmacologically active components and initially synthesized from intra-cocoon stages of *Phoneutria nigriventer* spiders. Its larval stage also possesses venom and its producing glands with a venomous apparatus. Similarly, PhTx1 plays important roles in the protection and survival of early developmental stages of P*honeutria* spiders (Silva *et al*., 2011).

Inhibition of voltage gated channels

Spider toxins are gating-modifiers and inhibit voltage-gated ion channels and alter the energetics of voltage-dependent gating. By using serial multi-scale molecular dynamics simulations it is proved that the toxin VSTx1 inhibits the archeabacterial voltage-gated potassium channel KvAP. It interacts with an isolated membrane-embedded VS (voltage sensor) domain. It partitioned between headgroup/water interface of the lipid bilayer before binding the VS (Wee *et al.,* 2010). Similarly, ProTx-I peptide, a venom toxin isolated from tarantula *Thrixopelma pruriens*, interact with voltage-gated ion channels and reduced Ba(2+) currents in human T-type voltage-gated Ca(2+) channels, i.e. Ca(v)3.1 (hCa(v)3.1). It shows 160-fold more potency than through hCa(v)3.2 channels (Ohkubo *et al.,* 2010). Similarly, two neurotoxic peptides, huwentoxin-III (HWTX-III) and hainantoxin-VI (HNTX-VI) isolated from *Selenocosmia huwena* and *Selenocosmia hainana* found in southern China. Both of these neurotoxic peptides, have shown diverse physiological effect and the mechanism of action (Wang *et al.,* 2010). Both the toxins have exclusively target the domain IV voltage-sensor to influence sodium channel inactivation. (Xiao *et al.,* 2010). Similarly, an amphipathic toxin from tarantula venom inhibits voltage-activated potassium (Kv) channels by binding to a critical helix-turn-helix motif. These toxins partition into membranes to bind the paddle motif and alter the activity of different types of ion channels (Jung *et al.,* 2010)

GxTX-1E is a neurotoxin recently isolated from *Plesiophrictus guangxiensis* venom that inhibits the Kv2.1 channel in pancreatic beta-cells. It shows sequences homology with tarantula toxins and interact with the voltage sensors in Kv channels with high affinity. Molecular structure of GxTx-1E contains an ICK motif, composed of beta-strands, and contains a prominent cluster of solvent-exposed hydrophobic residues surrounded by polar residues. The most striking structural differences between GxTX-1E and JZTX-III are found in the orientation between the first and second cysteine loops and the C-terminal region of the toxins. It proves that these highly specific regions of GxTX-1E are responsible for its high affinity (Lee *et al.,* 2010). Similarly, ProTx-II, a peptide toxin isolated from the venom of the tarantula spider *Thrixopelma pruriens*, dose-dependent activity and inhibit Ca(V)3.1 channels and cause a decrease in current (81.6% +/- 3.1% at -30 mV in 5 microM toxin), and do a positive shift in the voltage range of activation (+34.5 mV +/- 4.4 mV) (Edgerton *et al.,* 2010).

Receptor mediated responses

CaCNA1A gene product effect Ca++ concentration and knockdown gaglion neuron receptor mediated responces. These effects were successfully reversed by the Ca(v)2.1 blocker ω-agatoxin. A slight R192Q motion in this gene encodes for the a1 subunit of voltage-gated P/Q Ca2+ channels (Ca(v)2.1) and is associated with familial hemiplegic migraine-1. It significantly changes the structure and function of trigeminal neuron (P2X3) receptors, which are thought to be important contributors to migraine pain. Gene product effect Ca^{++}concentration and knockdown ganglion neurons receptor-mediated responses. The P2X3 receptor is intracellularly signaled by kinases and phosphatases ω agatoxin treatments, which strongly activate the CaMKII. The CaMKII inhibitor KN-93 blocked CaMKII. It is blocked by phosphorylation and the hyperesponsive P2X3 phenotype. Finally, pharmacological inhibitors of the phosphatase calcineurin normalized the enhanced P2X3 receptor responses of neurons and increased their serine phosphorylation. (Nair *et al.,* 2010).

Similarly, PhTx3-4 spider toxin inhibited capsaicin-stimulated release of glutamate in both calcium-dependent and -independent manners in spinal cord shnaptosomes. Contrary to this the conus toxins, ω-conotoxin MVIIA and ω-conotoxin MVIIC, only inhibited calcium-dependent glutamate release (Nunes *et al*., 2010). PhTx3-4, but not ? -conotoxin MVIIA or ω-conotoxin MVIIC, is able to inhibit the uptake of glutamate by synaptosomes, and this inhibition in turn leads to a decrease in the Ca(2+)-independent release of glutamate (Nunes *et al.,* 2010). Morespecifically, toxins PhTx3-4 and ω-conotoxins MVIIC and MVIIA block voltage-dependent calcium channels, and significantly inhibited the capsaicin-induced rise of intracellular calcium [Ca(2+)](i) in spinal cord synaptosomes. The inhibition of the calcium-independent glutamate release by PhTx3-4 suggests a potential role of this toxin to block abnormal glutamate release in pathological conditions such as pain (Gonçaves *et al.,* 2010). ω-conotoxin GVIA (omega-CgTX; 3 microM) or ω-agatoxin-TK (omega-Aga-TK; 200 nM) D(1) do receptor-mediated presynaptic inhibition of glutamate release onto cholinergic BF neurons these significantly change Ca++ channel structure and amplitude of EPSCs (Momiyama, 2010)

Similarly Earth *Tiger tarantula* toxin peptides selectively and irreversibly activates the capsaicin- and heat-sensitive channel, TRPV1. This high-avidity interaction derives from a unique tandem repeat structure of the toxin that endows it with an antibody-like bivalency. The "double-knot" toxin traps TRPV1 in the open state by interacting with residues in the presumptive pore-forming region of the channel, it causes conformational changes in the outer pore region of TRP channels during activation (Bohlen *et al.,* 2010). Similarly GsMTx4, a peptide inhibitor for mechanosensitive ion channels (MSCs), promoted neurite outgrowth from PC12 cells in the presence of NGF in a dose-dependent manner. It activates cation channels that were reversibly inhibited by GsMTx4. However, the inhibition of mechanosensitive channels by GsMTx4 may be a useful approach to accelerate regeneration of neurons in neurodegenerative diseases and spinal cord injury (Grishin *et al.,* 2010).

Similarly, a toxins isolated form Australian funnel-web spider termed delta-atracotoxins (delta-ACTX), consist of 42 amino acids and bind to voltage-gated sodium channels. It interacts with the voltage sensor S4 trans-membrane segment of alpha-subunit domain IV, thereby preventing its normal outward movement and concurrent conformational changes. It induce massive neurotransmitter release and causes clinical symptoms like muscle fasciculation, spasm, paresthesia , tachycardia diaphoresis etc. Similarly, α-latrotoxin (α-LTX), (132 kDa), isolated from black widow spiders, consist of a unique N-terminal sequence and a C-terminal part harboring multiple ankyrin-like repeats. It acts as a specific pre-synaptic receptors (Parodi *et al.,* 2010). More-specifically, α-LTX has shown its own tetramerization under physiological conditions and form Ca2+-permeable pores in pre-synaptic membranes of neuron cells. More-specifically, it's N terminus bind receptors and triggers intracellular signaling cascades that result in phospholipase C-mediated mobilization of presynaptic Ca2+ stores, or leads to the formation of tetrameric pore complexes, allowing extracellular Ca2+ to enter the presynaptic terminal (Parodi *et al.,* 2010). This toxin also triggers exocytosis and fulminant transmitter release at autonomic synapses provoke a clinical syndrome 'latrodectism',. This disorder is characterized by local and incapacitating pain, diaphoresis, muscle fasciculation, tremor and anxiety (Parodi *et al.,*2010)

Effect on acid-sensing ion channels

Spider toxins also interacted with acid-sensing ion channels (ASICs). These cationic channels which are activated by extracellular acidification and implicated in pain perception, ischemic stroke, mechanosensation, learning, and memory. These are a member of the degenerin/epithelial Na+ channel superfamily, expressed in the mammalian CNS, which acts as extracellular pH sensors in the central and peripheral nervous systems mainly in rat articular chondrocytes (Yuan *et al.,* 2010). Similarly, the tarantula venom psalmotoxin-1, is a specific blocker of ASIC1a homomers, that inhibits ASIC currents in BCs but not in O-LM cells (Weng *et al.,* 2010).

Normally, cells respond to a hyposmotic challenge by swelling and then returning toward the resting volume. This process is known as the regulatory volume decrease (RVD). Such types of sensors include cationic mechanosensitive ion channels which are opened by membrane tension (Hua *et al.,* 2010). GsMTx4, a specific inhibitor of cationic mechanosensitive channels and had no effect on RVD in primary rat astrocytes or Madin-Darby canine kidney (MDCK) cells, but it completely inhibit RVD and the associated Ca(2+) uptake in normal rat kidney (NRK-49F) cells in a dose-dependent manner. Similarly, purotoxin-1 (PT1), isolated from central Asian spider *Geolycosa* sp. showed selective inhibitory action on P2X3 receptors, which play a key role in pain perception. It completely slows down the removal of desensitization of these receptors. This peptide (CPT) shows potent antinociceptive properties in animals (Grishin *et al*., 2010).

Neurotoxins isolated from black widow and funnel-web spiders (Luch, 2010) and Chilean black widow spider (*Latrodectus mactans*) have shown exciting molecular effects in bovine spermatozoa and are sensitive to changes in K(+) concentration (30-140 mM) and to tetraethylammonium (TEA, 10-100 mM) (Parodi *et al.,* 2010). The application of the venom (7.5 microg/ml) blocks these K+ currents and then alters the passive properties of the plasma membrane (Parodi *et al.,* 2010).

GENOMIC STUDIES

Various molecular strategies such as transcriptomic, peptidomic, and genomic analyses were applied for high-throughput identification of tarantula-venom peptides from *H. hainanum* (Tang *et al.,* 2010). DNA sequencing studies done by Tang *et al.,* (2010) revealed about 420 peptide toxins and 272 peptide precursors from this spider species. After redundancy removal, 192 mature sequences were identified which is the largest number of peptide from a spider species (Tang *et al.,* 2010). Further on the basis of precursor sequence identity, peptide toxins from the tarantula *H. hainanum* venom were classified into 11 superfamilies. For such type of diversification both gene duplication and focal hypermutation are responsible (Tang *et al.,* 2010). Similarly another spider species *Ornithoctonus huwena* found in southern China was explored for identification of venom peptides. From which 41 novel unique transcripts encoding cellular proteins or other possible venom components were identified after annotated by KOG (eukaryotic orthologous group) and GO (gene ontology) methods (Jiang *et al.,* 2010). Among all a novel cellular transcript contig HWEFHP1 was found, which might be involved in the secretion of toxins in the venom glands. Further, comparison of the data obtained through a proteomic versus a transcriptomic approach, revealed 15 putative cystine knot toxins (CKTs) (Jiang *et al.,* 2010). Similarly transcriptome and venom analysis of the African spider *Citharischius crawshayi* was done by Diego-García *et al.,* (2010) using combined protocols of transcriptomics, venomics, and biological function (Diego-García *et al.,* 2010).

Figure 1. Alignment of spider toxins consensus. Alignment is made with appropriate gaps for selected spider toxins which are showing close homology. Amino acids in the bold are well considered

Alal_Latma	**MSKLFFVVFL**	**CLIISVFAIS**	**PADIGCTDIS**	**QADFDEKNNN**	**CIKCGEDGFG**
P105_Pletr	**AVKCIGWQET**	**CNGNPCCNE**	**CVMCECNIMG**	**QNCRCNHPKA**	**TNECE S…….**
P108_Pletr	**AVKCIGWQET**	**CNGKLPCCDG**	**CVMCECNIMG**	**QNCRCNHPKM**	**TSECGS……..**
P109_pletrs	**CAKHSETCKN**	GNCC TCTQYR	GKDEPNECRR	**GTHGQRCQCV**	**MKIMKH……**
P110_Pletr	**GCKGFLVKCD**	SNSECCKTAI	VKGKKKQLSC	**LCGAWGAGCS**	**CSFRCGNRC**
P111_Pletr	**EVKCIGWQEY**	CRGNLPCCDD	CVMCECNIMG	**QNCRCNIHPRI**	**TSECGS……..**
P112_Pletr	**AVKCIGWQET**	CNGNLPCCNE	CVMCECNIMG	**QNCRCNHPKA**	**TNECE……..**
P113_Pletr	**ALKCQGWVDY**	CNGNVECCNE	CVMY……	……	……
P114_Pletr	**AVKCIGWQET**	CNGKLPCCDG	CVMCECNIMG	**QNCRCNHPKA**	**TSECES……..**
PITX_Pletr	**ADCSATGDTC**	DHTKKCCDDC	YTCRCGTPWG	**ANCRCDYYKA**	**RCDT……..**
Tx1a_Ageap	**AKALPPGSVC**	DGNESDCKCY	GKWHKCRCPW	**KWHFTGEGPC**	**CEKGMKHTC**
Tx1b_Ageap	**ERGLPEGAEEC**	DGNESDCKCA	GAWIKCRCPP	**MWHING……**	**……**
Tx21_Phoni	**ATCAGQDKPC**	KETCDCCGER	GECVCALSYE	**GKYRCICRQG**	**NFLIAWHKLA**
Tx25_Phoni	**ATCAGQDQTC**	KVTCDCCGER	GECVCGGPCI	**CRQGNFLIAA**	**YKLASCKCK..**
Tx26_Phoni	**ATCAGQDQPC**	**KETCDCCGER**	**GECVGGPCI**	**CROGYEWIA**	**YKLANCKK…**
Tx29_Phoni	**SFCIPFKPCK**	**SDENCCKKFK**	**CKTTGIVKLC**	……	……
Tx3_Phoni	**GCIGRNESQK**	**KDNVYKFKE**	……	……	……
Tx4a_Ageap	**KKKCIAKDYG**	**RCKWGGTPCC**	**RGRGCICSIM**	**GTNCECKPRL**	**IMEGLGLA**
Tx4b_Ageap	**MLKCMTLLIT**	**AIAVVTFVVA**	**RQEESAEFNE**	**VEESREDNCI**	**AEDYGKCTWG**
Tx11Phoni	**AELTSCFPVG**	**HECDGDASNC**	**NCCGDDVYCG**	**CGWGRWNCKC**	**KVADQSYAYG**
Txm1_Ageap	**ECVPENGHCR**	**DWYDECCEGF**	**YCSCRQPPKC**	**ICRNNN……**	……
Txm1_Holcu	**SCVGEYGRCR**	**SAYEDCCDGY**	**YCNCSOPPYC**	**LCRNNN……**	……
Txm2_Ageap	**ECATKNKRCA**	**DWAGPWCCDG**	**LYCSCRSYPG**	**CMERPSS……**	……
Txm3_Ageap	**ADCVGDGQKC**	ADWFGPYCCS	GYYCSCRSMP	**YCRCRSDS……**	……
Txm3_Holcu	**ADCVGDGQKC**	ADWFGPYCCS	GYYCSCRSMP	**YCRCRSDS……**	……
Txm4_Ageap	**ACVGENQQCA**	DWAGPHCCDG	YYCTCRYFPK	**CICRNNN……**	……
Txm5_Ageap	**ACVGENKQCA**	DWAGPHCCDG	YYCTCRYFPK	**CICRNNN……**	……
Txm6-Ageap	**DCVGESQQCA**	**DWAGPHCCDG**	**YYCTCRYFPK**	**CICVNNN……**	……
Txo2_Ageap	**GCIEIGGDCD**	**GYOEKSYCQC**	**CRNNGFCS…**	……	……
Txo3_Ageap	**SCIDIGGDCD**	**GEKDDCQCCR**	**RNGYCSCYSL**	**FGYLKSGCKC**	**VVGTSAEFQG**
Txp1_Aptsc	**EIAQNLGSGI**	**PHIRTKLPNG**	**QWCKTPGDLC**	**SSRSECCKAE**	**DSVTYSSGCS**
Txp3_Aptsc	**CNSKGTPCTN**	**ADECCGGKCA**	**YNVWNCIGGG**	**CSKTCGY……**	……
Txp4_Aptsc	**EIPQNLGSGI**	PHDRIKLPNG	QWCKTPGDLC	**SSSSECCKAK**	**HSNSVTYASF**
Txp6_Aptsc	**EIPQNLGSGI**	PHDKIKLPNG	QWCKTPGDLC	**SSSSECCKAK**	**HSNSVTYASF**
Txp7_Aptsc	**WLGCARVKEA**	CGPWEWPCCS	GLKCDGSECH	**PQ……**	……
Txp9_Aptsc	**EIPQNLGSDI**	**PHDIIKLPNG**	**QWCKTPGALC**	**SSRSECCKAK**	**HSDSVTYSSG**
Txr0_Atrro	**CAKKRNWCGK**	NEDCCCPMKC	IYAWYNQQGS	**CQTTITGLFK**	**KC……**
Txvs_Atrve	**CAKKRNWCGK**	TEDCCCPMKC	VYAWYNEQGS	**CQSTISALWK**	**KC……**
Consensus	**ACKCIGGQCC**	**-NGC-CCC-G**	**GYCCCCG-MG**	**CNCRCNCPK-**	**TSECGGSYASG**

INSECTICIDAL ACTIVITY OF SPIDER TOXINS

Insects are the main natural targets of spiders, which have shown high toxicity. These are lonely group which are being eaten up by the spiders. It could be used for development of insecticide (Grolleau *et al.,* 2001). Though there exists a diversity in spiders, but few of them are venomous and highly dangerous to people. Most of the spider toxins cause irreversible paralysis in lepidopteran insects by massive transmitter release, which is mediated by glutamate receptors from presynaptic stores at neuromuscular junction (Skinner *et al.,* 1989). Argiotoxin isolated from the orb-weaving spider *Argiope lobata* (Grishin *et al.,* 2010) cause reversible blockage of cation selective quisqualic acid sensitive glutamate receptor of the Locust (Batemab *et al.,* 1985). It inhibits L-glutamate receptor and associated ion channels in the vertebrate central nervous system and the invertebrate neuromuscular junction (Kawai *et al.,*1982; Kawai *et al.,* 1983; Michaelis *et al.,* 1984; Saito *et al.,* 1985; Jackson *et al.,* 1987). Similarly some insecticidal peptides have been isolated from funnel web spider *Hololena curta,* which also generate quick paralysis in cricket *Acheta domestica* and cause irreversible blockage of pre and postsynaptic neuromuscular transmission mediated by glutamic acid receptors (Grolleau *et al.,* 2001). Few spider species present a real threat to humans (Jackson and Usherwood, 1988) (Table 1).

CONCLUSION

Spider toxins show multiple symptoms in patients and target various ion channels. Initially, spider venom expresses various local and general effects such as pain, swelling, sweating, blistering, bleeding, necrosis, headache, vomiting, abdominal pain, hypertension, hypotension, cardiac arrhythmias and arrest, convulsions, collapse, shock. Afetr severe envenomation it causes specific systemic effects like paralytic neuroexcitatory, neurotoxic and myotoxic, interference with coagulation, hemorrhagic activity, renal toxicity, cardiac toxicity. For removal of above effects anti-venom is considered as the last remedy. However, anti-venom is available only for a limited range of species, not for all dangerous species, is in short supply in some areas of highest need, and in many cases, is supported by historical precedent rather than modern controlled trials (White, 2010). Spiders possess lethal components in the search for cures and understanding of their mechanisms of action. Ion channels have emerged as targets for many venom peptides, providing researchers highly selective and potent molecular probes that have proved invaluable in unraveling ion channel structure and function.

Protein toxins from spider venoms are of interest to a wide range of biologists due to their diverse applications in medicine, neuroscience, pharmacology, drug discovery and agriculture. For this purpose, research groups engaged in venoms-based research, enabling them to easily manage and securely store data during the process of toxin discovery; and a detailed user manual is now available (Herzig *et al.,* 2011). Studies on toxin-receptor interactions will certainly help in development of peptide therapeutics and mainly in drug development. Due to their selective binding to ion channels toxin peptides can be used as potent molecular probes to determine structure and function of ion channels. Further studies related to transcriptome and gene finding help to discover new components from spider venom glands of very high therapeutic potential

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