International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2016.126.135

Review Article

Immunomodulatory and Therapeutic Potential of Zootoxins (Venom and Toxins) on the Way Towards Designing and Developing Novel Drugs/Medicines: An Overview

[1]I. Mohanty, [2]K. Arunvikram, [1]D. Behera, [3]A. Arun Prince Milton, [4]G. Elaiyaraja, [5]G. Rajesh and [6]K. Dhama

[1]Department of Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Orissa University of Agriculture and Technology, Bhubaneswar 751003, Orissa, India
[2]Division of Pharmacology and Toxicology,
[3]Division of Veterinary Public Health,
[4]Immunology Section,
[5]Division of Physiology and Climatology,
[6]Division of Palhology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly 243122, Uttar Pradesh, India

Abstract

The evolution of poison and venom had made the animal body system to deal effectively with defense mechanism primarily by molecular means. These chemical defences target the cell membrane receptors, block the physiological systems in body and cause paralysis. Evolution around years, led to the development of these peptides with effective functional properties that made them more selective and potent, but immunogenically poor, provide prolonged action and potent effect on preys. When a venom or toxin is enriched with these functionally effective peptides form 3D structure that are linked by disulphide brides. This structure is highly stable and they specifically target GPCRs, ion channels and other membrane receptors and it was proved to have indispensable pharmacological properties. The first drug Captopril discovered against hypertension was isolated from Brazilian viper, *Bothrops juraraca.* It is one of the most popular and accepted antihypertensive drug used world wide now-a-days. Since then peptides isolated from snake, scorpion, spider, bee and sea anemone toxin have proved to display potential immunomodulatory effects and were useful in treating rheumatoid arthritis, multiple sclerosis, lupus and psoriasis including autoimmune diseases in human. The present article in not intended to be a definitive review of entire field of zootoxins, but rather an overview, which emphasize on recent developments made in the field of zootoxins (venoms and toxins), their role in the treatment of diseases with a special focus towards exploring their potent immunodulatory and therapeutic potential in the field of drug development. Advances in the fields of analytic chemistry, molecular biotechnology and biochemistry are now making it possible to isolate and purify individual components, using a minute amount of a toxin.

Key words: Zootoxin, icthyotoxin, venom-based cure, immunomodulatory effects

Received: October 25, 2015 **Accepted:** December 11, 2015 **Published:** January 15, 2016

Citation: I. Mohanty, K. Arunvikram, D. Behera, A. Arun Prince Milton, G. Elaiyaraja, G. Rajesh and K. Dhama, 2016. Immunomodulatory and therapeutic potential of zootoxins (venom and toxins) on the way towards designing and developing novel drugs/medicines: An overview. Int. J. Pharmacol., 12: 126-135.

Corresponding Author: K. Dhama, Division of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly 243122, Uttar Pradesh, India

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Since evolution, living system that is animals and humans developed a variety of adaptation ways for feeding and defense, which are the two basic aspects of life. The largest mammal of earth, elephants have a well developed tusks that helps in feeding also serves as a defense. Also reptiles like snakes and other animals have different evolutionary derived strategy to deal with feeding and defense. Animals venom have three potent activities such as prey-immobilization, prey digestion and defense (Wigger *et al*., 2002; Morgenstern and King, 2013).

When an animal posses special features such as stings, nematocysts, a special teeth, arrows or hairs to deliver the venom into the prey, then it is said to be venomous (Ericsson *et al*., 2006). Reptiles such as snakes, few lizards, insects and flies such as spiders and bees, sea creatres such as cone snails and octopuses produce toxic substances that help them in catching or trapping the prey and also as a self defense to protect themselves from getting preyed. In contrast, poisonous animals, lack any specific apparatus for injecting venom and toxins are distribted in their tissues which get activated once the animal is being ingested (Warrell, 2003). One of the venomous mammal is male duck-billed platypus in which the venom is carried inside their ankle spurs. Insights at molecular studies tells that the peptides in the toxin once injected into the vein will target the cardiac, nervous or respiratory systems in the the body, leading to blockage of the system followed by paralysis and death. These toxic peptides act precisely on ion channels, G-protein coupled receptors and other cell membrane receptors. Gradually, venom alongwith its various components had been known to act independently in various animal groups and have been reported to be specific for species, subspecies or even geographic-variation. These species- specific effects of venom, makes it difficult for researchers to transfer observations from animals to humans (Junghanss and Bodio, 1996). The basic molecular configuration of the venom remain unchanged though the years of evolution has made minor changes to these toxic compounds. The key molecules from blood, brain, digestive tract in the body have been proposed by nature to serve animals for predation or protection. Zootoxin is the only phenomenon in the field of medicine, which has fascinated both researchers and common men by enriching our knowledge in basic and applied science. As per WHO (2015), the cases of snake envenomisation alone may be around 2.5 million and number of death due to snake bite to be approx 20-125 thousand every year.

Animal venoms are conglomers of 20-25 different molecules and have peptides of 30-80 amino acid residues. The poisonous animal species have alkaloids in predominance that exhibit strong biological effects though they are small molecules. Table 1 represents a brief overview of zootoxins along with their respective sources, mechanism of action and chemical constituents. Paradoxically, the same venom which is a deadly hazard can be exploited to synthesise valuable medicine. Venoms and poisons contain pure toxic peptides which almost have specific action on biological systems making them an essential source for design and synthesis of therapeutic agents (Gomes *et al*., 2010). Marine species produce many biologically active peptides such as antimicrobial peptides (Matsunaga *et al*., 1985), neurotoxins (Tu, 1974), anti-tmour and anti-viral (Rinehart *et al*., 1981), cardiotonic peptide (Norton *et al*., 1976) and cardiotoxins (Bernheimer *et al*., 1982). The first of angiotensin converting enzyme i.e., captopril, a drug commonly used against hypertension and myocardial infarction owes it's discovery to Brazilian viper, *Bothrops juraraca*. The present review reflects the recent developments made in the field of uses of zootoxins (venoms and toxins), their role in the treatment of diseases and disorders, cancer, autoimmune diseases, arthritis and other beneficial health applications with a special focus towards exploring their potent immunodulatory and therapeutic potentials in the field of drug development.

Venom based curative therapies-historical developments:

Venom-based cures and their use dates back to ancient era as evident from their mention in Sanskrit scriptures *Charak samhita*, *Vagbata samita* and *Saranghara samita* (Pal *et al*., 2002; Gomes *et al*., 2010). It is believed that during the primedivial period, Mithradates VI of Pontus whose wounds in battle field are healed by administration of steppe viper venom by shamans (Now-a-days crystallized snake venom is exported from Azerbaijan as a medicine). In indian medicine cobra venom, has been useful in Dushyodara and Jalodara (ascites). In unani field of medicine cobra venom is being used as hepatic stimulant, tonic, aphrodiasic and for resuscitation in collapsed conditions (Debnath *et al*., 1972). Venom of spider, bee and snake are routinely used in homeopathy (Pal *et al*., 2002). Bee venom was by hyppocrates to treat arthritis and joint pain. But the curative dose which he used was just within the limit of the pathogenic dose. The development in science of synthesising therapeutic peptides from venoms started in 1960s, when Hugh Alistair Reid, an English clinician who suggested that the venom extracted from the Malayan pit viper (*Ancistrodon rhodostoma*) may be used to treat deep-vein thrombosis condition (Hawgood, 1998). In the year 1968, Hugh named this defibrinating derivative of *A. rhodostoma* venom as Arvin (ancrod) which

Table 1: Zootozins, their sources and mechanism of action

Animal	Zootoxins/chemical compound	Mechanism of action	References
Jararacussu (*Bothrops jararacussu*)	Phospholipase A2 (PLA2)	Decreases sarcoplasmic Ca^{2+}-ATPase	Ayres *et al.* (2015)
Black mamba (*Dendroaspis polylepis*)	Calciseptine (CAS)	Inactivate L type Ca channel	Moeller *et al.* (2012)
Australian tiger snake (*Notechis scutatus*)	Notexin (Ntx)	Promotes the enzymatic hyd rolysis of sarcolemmal phospholipids which results in membrane damage and Ca^{2+} influx	Dixon and Harris (1996)
Cobra (*Naja atra*)	Cobrotoxin (CBTX)	Post-synaptic non-depolarising block	Sribar *et al.* (2003)
Krait (*Bungarus candidus*)	Candoxin (CDX)	Bind to post-synaptic muscle nAChRs produces reversible, non-depolarising block	Nirthanan *et al.* (2003)
Russell's viper (*Daboia russelii*)	Viperotoxin-F (RV-4/RV-7)	Pre-synaptic block	Hodgson and Wickramaratna (2002)
Mamba (*Dendroaspis angusticeps*)	Calcicludine (CaC)*	Muscarinic effects by binding to muscarinic AChRs and also inactivate L type Ca channel	Rajagopalan *et al.* (2009) and Moeller *et al.* (2012)
Rattle snake (*Crotalus durissus*)	Phospholipase A2 (PLA2)	Post-synaptic effect by desensitization of nAChR	Doley and Kini (2009 and Sampaio *et al.* (2010)
Funnel web spiders (*Atrax robustus*)	Robustoxin/d-Atracotoxin (d-ACTX)	Induces spontaneous, repetitive firing and prolongation of action potentials, prolonged acetylcholine release from both somatic and autonomic nerve endings	Gupta (2007)
Widow-spider (*Latrodectus mactans*)	α-latrotoxin (α-LTX)	α-LTX interacts with neurexins and latrophilins on the neuronal membrane, induces pore formation on the membrane, causes exocytosis, followed by massive release and then depletion of acetylcholine and norepinephrine at postganglionic sympathetic synapses	
Brown recluse spider (*Loxesceles reclusa*)	Sphingomyelinase D (SMASED)	Stimulates cytotaxis atthe site of envenomation, inactivates serum hemolytic complement leading to intravascular coagulation, occlusion of small capillaries, tissue necrosis, systemic depletion of clotting factors (VII, IX, XI, XII) and platelet activation	Gupta (2007)
Trinidad tarantura (*Psalmopoeus cambridgei*)	Psalmotoxin (PcTx1)	Causes desensitization of ASIC1 (Acid Sensing Ion Channel 1)	Escoubas *et al.* (2000)
Deathstalker scorpion/ Israeli yellow scorpion (*Leiurus quinquestriatus hebraeus*)	Chlorotoxin (CTX), Charybdotoxin (CHTX), Scyllatoxin, Agitoxins (AgTx) Type I, II, III	Increases Ca influx into cardiocytes through L-type Ca channels, inhibits the chloride ion channel	Ariesaadia *et al.* (1996) and Soroceanu *et al.* (1998)
Giant forest scorpions (*Heterometrus fulvipes*)	κ-Hefutoxin 1 (Heteroscorpine-1)	Inhibits Kv1.2, Kv1.3 and slows down the activation of Kv1.3	Meves (2008)
Wasp	Mastoparan (MAS)	Acts as a nonspecific secretagogue primarily involves exocytosis, causes histamine release from mast cells, serotonin and catecholamine release from platelets and chromaffin cells, prolactin release from anterior pituitary respectively, inhibits K_{ATP} both vascular and smooth muscle cells	Eddlestone *et al.* (1995)
Honey bee venom (*Apis mellifera*)	Apamin (APA)	Inhibits SK2, SK3(small conductance calcium channels)	Santos-Torres *et al.* (2011)
	Melittin (MLT)	Act as cell membrane lytic factor, inhibits protein kinase C, Ca^{2+}/calmodulin-dependent protein kinase II, myosin light chain kinase and Na^{+}/K^{+}-ATPase	Yang and Carrasquer (1997)
Sea anemone (*Stichodactyla gigantea*)	Gigantoxin I (epidermal growth factor -like toxin), II, III	Activate TRPV1 indirectly pathway involving ECF receptor via PLA2 and arachidonic acid	Chen *et al.* (2002) and Cuypers *et al.* (2011)
Striped blister beetle (*Epicauta vittata*)	Cantharidin	Inhibits protein phosphatase 2A, resulting in disruption of signal transduction and cell metabolism	Stair and Plumlee (2004)
Fireflies (*Photinus* spp.)	Lucibufagins (LBG)	Inhibit sodium–potassium ATPase activity in the myocardial cell membrane	Brubacher *et al.* (1999)
Red imported fire ant (*Solenopsis invicta*)	Solenopsins and piperidine	Cytotoxic, hemolytic, fungicidal, insecticidal and bactericidal properties	Gupta (2007)
Toad (*Bufo marinus*)	Bufogenins	Inhibit sodium-potassium ATPase	Gupta (2007)
Gila monsters (*Heloderma suspectum*)	Gilatoxin (GTX)	Lethal factor, kallikrein like activity, pain, hypotension	Gupta (2007)
	Helodermin, Helospectin I and II	Vasodilation, hypotension	Grundemar and Hogestatt (1990)
Australian paralysis tick (*Ixodes holocyclus*)	Holocyclotoxin	Inhibits acetylcholine release at the neuromuscular junction	Grattan-Smith *et al.* (1997)

was used clinically as a clot-busting drug in Europe. These days Arvin has been substituted by other venom anticoagulants. In 1970's, Brazilian pit viper (*Bothrops jararaca*) venom led to the development of a class of antihypertensives, ACE inhibitors. Finally, in 1975 a more synthetic version, captopril the first oral drug was approved as an antihypertensive in human (Blankley, 1985). Recently prialt and byetta has replaced catptopril in the market after integrillin and aggrastat.

Immunomodulatory potential of snake venom: There are nearly more than 2000 species of snakes in the world among which approximately 300 are venomous belonging to families, Elapidae (coral snake, cobra, krait, tiger snake, mamba and taipan), Colubridae (boomslang), Hydrophidae (sea snakes), Viperidae (old world vipers, saw scaled viper, Gaboon viper, Russell's viper and puff adder) and Crotalidae (pit vipers, cotton mouth, copper head and rattle snakes) (Karalliedde, 1995). Local and systemic hemorrhages are the classic indication of envenoming by the viperid snakes. Snake venom metalloproteinases (SVMPs) in the microvasculature are specifically in capillaries responsible for the hemorrhagic activity (Herrera *et al*., 2015). Venoms generally aim to cause paralysis leading to death, but some venoms also elicit acute pain. The venoms target somatosensory nerve terminals and stimulate the nociceptive neural pathways (Bohlen and Julius, 2012).

Naja Naja Atra Venom (NNAV) regulates the immune system by precise increase in Th1 and Th2 cytokines (IFN-γ and IL-4, respectively) by secretion and inhibition of Th17 cytokine (IL-17) production which in turn raises the innate and humoral immune responses and inhibits the CD4 Th17 and CD8 T cell actions, thus implying a possible therapeutic agent for autoimmune diseases (Kou *et al*., 2014). *Bungarus caeruleus* snake venom (BCV) treatment significantly increases the production of TNF-α, IFN-γ, ROS, NO mediated through immunomodulatory activity associating the macrophages (Bhattacharya *et al*., 2013). The venom from *Crotalus durissus cascavella* and *Bothrops erythromelas* induces a distinct immunomodulatory effect *in vitro* through production of NO and cytokines. *Bothrops erythromelas* stimulates a proinflammatory response whereas *C. durissus cascavella* stimulates an anti-inflammatory effect (Luna *et al*., 2011). In an *in vitro* study conducted by Ribeiro *et al*. (2014) in PBMC's of human, the *C. durissus collineatus* venom lead to increased production of IL-10 and TNF that resulted in cell death suggesting their proinflammatory and anti inflammatory activity. Hannalgesin isolated from *Ophiophagus hannah* venom exerts its effect by binding to the SS1 or SS2 subunit of the sodium channel (Pu *et al*., 1995). The two main components phospholipases A_2 and metalloproteases of Bothrops snake venom mediates the inflammatory response (Teixeira *et al*., 2003, 2009; 2005; Correa-Netto *et al*., 2010). Studies also suggest that *Bothrops asper* activates the complement system (Farsky *et al*., 2000) Batroxobin, inhibits the conversion of fibrinogen to fibrin is a serine protease isolated from *Bothrops atrox moojeni* venom. Bothrojaracin, isolated from *Bothrops jararaca* exerts its anti-thrombin activity by binding to the two thrombin anion binding exosites I and II at fibrinogen and antithrombin respectively (Zingali *et al*., 2006). Lebecetin, a C-type lectin-like protein exclusively binds to the platelet anti-glycoprotein Ib (GP1b) was isolated from *Macrovipera lebetina*. Ecarin is a 1A prothrombin activator metalloproteinase isolated from *Echis carinatus* venom that aids in the detection of von Willebrand disease (Schieck *et al*., 1972). Pseutarin C, extracted from venom of *Pseudonaja textiles* by incitement of prothombin converts prothrombin to thrombin. Salmosin, isolated from *Gloydius ussuriensis* venom strongly inhibits tumor-derived angiogenesis, attachment and generation of tumor cells. Rhodostomin, hampers angiogenesis induced by basic fibroblast growth factor and abolished the murine melanoma B16-F10 tumor growth is derived from the venom of *Calloselasma rhodostoma* (Yeh *et al*., 2001). Textilinin, a reversible plasmin inhibitor and can be harvested as an anti-bleeding agent is a highly potent venom of from Australian brown snake *Pseudonaja textilis* (Millers *et al*., 2009). Arvin extracted from Malaysian pit viper *Caloselasma rhodostoma* suppress the chronic inflammatory responses mainly arthritis (Ford *et al*., 1970).

Immunomodulatory potential of scorpion venom: Scorpion envenomisation leads to induction of systemic immune response and augment the excitability of muscle and nerve cells by release of noradrenaline, acetylcholine and serotonin or action on ion channels (Adam and Weiss, 1959). The alpha and beta scorpion toxins prolong the action potential through delaying inactivation of sodium channels, but beta toxins in addition also affect the activation of sodium channels. The sodium channel is activated at membrane potential level in which the channel would be regularly closed (Jover *et al*., 1980). Mexican scorpion toxin was the first toxin observed to block voltage-dependent potassium channels. Chloride channels are also serve as receptors for scorpion toxin.

Harald Sontheimer isolated the peptide chlorotoxin from *Leiurus quinquestriatus* (the giant Israeli Scorpion) venom which specifically killed only the cancerous cells leaving the

healthy cells intact, thus exploring it as a potent anticancer drug (Soroceanu *et al*., 1998). Agitoxin-2, anuroctoxin, charybdotoxin (ChTX), hongotoxin, kaliotoxin, margatoxin (MgTX), noxiustoxin (NTX) and orthochirus scrobiculosus toxin 1 (OSK1) also block K_V1.3 channels (Wulff and Zhorov, 2008; Zhao *et al*., 2015).

Tityus serrulatus scorpion envenomation induces the inflammatory mediators which affect the local and systematic immune response. *Tityus serrulatus* (TsV) toxins Ts1 and Ts6 induced the production of NO, Interleukin (IL)-6 and tumor necrosis factor alpha (TNF-α) in combination with lipopolysaccharide (LPS) in stimulated J774.1 cells, however, Ts2 toxin and LPS combination showed opposite to this effect. Also, Ts2 alone showed anti-infllamatory effect by induction of IL-10 (Zoccal *et al*., 2011). The Ts1 has a crucial immunomodulatory response on macrophages (Petricevich *et al*., 2007). The Ts2 (TsTX-III) and Ts6 (TsTX-IV) depend on lipid mediator and cytokine production mechanism to induce inflammation (Zoccal *et al*., 2013). The Ts2 may show a regulatory role and Ts6 a pro-inflammatory activity, hence, may be harnessed as a therapeutic agent for immunological disorders. Similarly, *Tityus serrulatus* scorpion crude venom (Tsv) injected subcutaneously in mice induced the blood neutrophils recruitment and serum IL-6, IL-10 and TNF-α (Fialho *et al*., 2011). Casella-Martins *et al*. (2015) studied that TsV was found to activate peritoneal macrophages of mouse expressing the lymphocytic role in envenomation. HsTX1 toxin, isolated from the *Heterometrus spinnifer* scorpion, reveals potentially attractive candidature for the treatment of autoimmune diseases i.e., multiple sclerosis and rheumatoid arthritis, as it has been shown to block K_V1.3 channels (Rashid *et al*., 2014). A potent immunosuppressive toxin Kaliotoxin (KTX) is beneficially effective on the neurological symptoms of autoimmune encephalomyelitis and treating bone resorption in periodontitis. The KTX that blocks Kv1.3 might establish a potential therapy to prevent alveolar bone injury in periodontal disease (Zhao *et al*., 2015). Indian red scorpion venom was reported to have the property to treat Freunds complete adjuvant induced arthritis in rat model (Nipate *et al*., 2014). Androctonus australis hector venom (Aah venom) of scorpion induces the release of cytokines such as IL-6, TNF-alph a leading to tissue damage (Raouraoua-Boukari *et al*., 2012).

Immunomodulatory potential of spider venom: Alpha latrotoxin from black widow spider venom, cause depletion of synaptic vesicles at neurotransmitter junction. This mechanism of action is exerted by the polypeptide toxins of the venom that acts on presynaptic nerve terminals leading to extensive release of transmitter from the cationic channels (Clark *et al*., 1972). Similarly, the Agatoxins isolated from Agelenidae (Australian funnel-web spider) affects synaptic transmission acting on calcium channels, blocking access of calcium into presynaptic terminals and inhibiting release of inhibitory transmitters such as glycine and GABA (Adams *et al*., 1990). Heminecrolysin, a sphingomyelinase D (SMaseD), released during *Hemiscorpius lepturus* (H.) envenomation causes the major pathological effects in man. *Lycosa singoriensis*, a wolf spider more common in north western regions of china produces rashes and pain in animals and humans around the site of bite (Lu and Zhang, 2001). Antimicrobial peptides lycotoxin I ans II forms pore in the synaptsomoses leading to outflow of calcium ions (Yan and Adams, 1998). In addition these peptides also has antimicrobial property that inhibits the growth of microbes (Liu *et al*., 2009). The exposure of phosphatidylserine effect on human nucleated Jurkat T cells, stimulates pro-inflammatory secretions (TNF-α, IL-6) and anti-inflammatory cytokines (IL-10) and stimulates a disseminated intravascular coagulation effect on chorioallantoic membrane inoculated chick embryo model (Borchani *et al*., 2013). *Lachesana tarabaevi* spider venom, Latarcins (Ltc) is a linear cytolytic peptide which also has been reported to reveal immunomodulatory effect (Dubovskii *et al*., 2015).

Immunomodulatory potential of bee toxins: Bee venom consists of histamine, mellitin, apamin, adolapin and phospholipase A2 causing cytolytic effect on skin mast cells leads to release of histamine (Markovic and Rexova, 1963). A high concentration of >100 μg mL^{-1} causes lymphocyte instability while lower concentration of same don't cause oxidative damage. This bee venom therapy has been since time immemorial to alleviate pain in rheumatoid arthritis and multiple sclerosis (Mohammadi *et al*., 2015). Mellitin which comprises of 50% of the dry weight of bee venom exerts its anti-arthritis effects by inhibition of nuclear factor kappaβ (NF-κβ), decrease in the production of pro-inflammatory cytokines (TNF-α, IL-6 and IL-1β), cyclooxygenase and phospholipase enzymes and Reactive Oxygen Species (ROS) (Mohammadi *et al*., 2015). It also suppresses the expression of Toll-like receptor-2 (TLR-2) and CD14; reduces the binding activity of Activator Protein (AP-1) and nuclear factor-κβ (NF-κβ) and decreased the production of TNF-α and IL-1β (An *et al*., 2014). It accelerates the differentiation of FOXP3-expressing cells both from fresh CD4 T cells and

[1]www.kinetabio.com/autoimmunediseases.html

mature CD4 thymocytes, a tract that may commit to the VIT s space to spread circulating Tregs in allergic individuals (Caramalho *et al*., 2015). In another study, the bee venom and mellitin showed its anti-cancer effect by inducing the apoptotic cell death of SKOV3 and PA-1 human ovarian cancer cells through enhaced expression of DR3, DR4 and DR6, in addition it inhibit the STAT3 pathway (Jo *et al*., 2012).

Hymenoptera stings often leads to death by immune dysfunction thus by the venom allergens react with cell-bound IgE and induces the huge release of histamine, prostaglandins, leukotrienes, chemotactic factors and a myriad of many different factors (Wasserman, 1983). Apitherapy (opitoxin) is used to treat the patients who suffer from inflammatory or degenerative diseases such as arthritis. It provides a soothing relief against arthritis and other systemic inflammations. Moreover, bee venom toxin can soften the scar tissues and break them down, has a local anti-inflammatory effect and can treat both acute injuries such as tendonitis and chronic neck pain. Also apitoxin was found to treat cancer. It was suggested that the venom peptides target the tumour cells and the cell exhibits its cytotoxic on activation by these peptides and establishes its anti-tumour activity, also induces apoptosis of the tumour cell (Orsolic, 2012)

Immunomodulatory potential of marine snail and sea anemone venom: Conantokins and conotoxins from snail venom helps to alleviate the pain in people with epileptic seizures and cancer, respectively. The α-conopeptides target particular subtypes of nicotinic receptors (Myers *et al*., 1991), also both are protective against Parkinson's and Alzheimer's diseases, nicotine addiction and depression (Livett *et al*., 2004). The δ-conopeptides delay inactivation (Shon *et al*., 1994) whereas μ- and μO-conopeptides restrict voltage-gated sodium channels (Na_V) (McIntosh *et al*., 1995; Cruz *et al*., 1989), σ-conopeptides block 5-HT_3Rs (type 3 serotonin receptors) (England *et al*., 1998), similarly ω-conopeptides block the subtypes of voltage-gated calcium channels (Ca_V) (Olivera *et al*., 1984; McCleskey *et al*., 1987), likewise κ- and κα-conopeptides block voltage-gated "Shaker" potassium channels (K_V) (Olivera *et al*., 1984), conantokins inhibit N-methyl-D-aspartate receptors (NMDARs) (Jimenez *et al*., 2002) and norepinephrine transporter got inhibited by χ-conopeptides, conopressins and contulakin-G are act as an agonists at vasopressin receptors (Cruz *et al*., 1987) and neurotensin receptors (Craig *et al*., 1999) respectively, whereas the ρ-conopeptides inhibit α-adrenergic receptors.

Stichodactyla toxin (ShK) is a peptide toxin isolated from sea anemone (*Stichodactyla helianthus*) that restricts the voltage-gated potassium (Kv) channels i.e., Kv1.1, Kv1.3, Kv1.6, Kv3.2 and KCa3.1. The ShK is a potent immunosuppressant which can be exploited for the treatment of autoimmune diseases such as multiple sclerosis (Beeton *et al*., 2011). Similary, The venom isolated from sun anemone has also been useful against human autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, psoriasis and lupus. Moreover, the Dalazatide (ShK-186) a reconfigured peptide can be used against multiple autoimmune diseases like rheumatoid arthritis, psoriasis, atopic dermatitis, psoriatic arthritis, multiple sclerosis, inflammatory bowel diseases, lupus, type 1 diabetes mellitus, asthma, autoimmune uveitis and vasculitis[1].

CONCLUSION

All venoms and toxins (zootoxins) have a multifaceted and multitasking effect. In the evolutionary struggle between competing sets of co-evolving species, i.e., race between predator and prey, weapons and defenses are constantly tugged. However, deadly venom also is enriched with properties that make it valuable for therapy. Venom or toxins often act specifically on the particular target in the same manner just like a lock and key fitting model for therapeutic cure. Currently, it's a challenge for scientists and health professionals to discover the active principle of the toxin that hits only the certain target and then exploit the same active molecule to design a cure for deadly diseases. New molecules for the treatments of autoimmune diseases, diabetes, heart diseases, cancer and chronic pain could be available within a decade. It won't be an exaggeration to state that venom will serve as a stepping stone to future medicine. Finally, the peptides in zootoxins have enriched us a boon in the field of health and medicine.

REFERENCES

Adam, K.R. and C. Weiss, 1959. Actions of scorpion venom on skeletal muscle. Br. J. Pharmacol. Chemother., 14: 334-339.

Adams, M.E., V.P. Bindokas, L. Hasegawa and V.J. Venema, 1990. Omega-agatoxins: Novel calcium channel antagonists of two subtypes from funnel web spider (*Agelenopsis aperta*) venom. J. Biol. Chem., 265: 861-867.

An, H.J., W.R. Lee, K.H. Kim, J.Y. Kim and S.J. Lee *et al*., 2014. Inhibitory effects of bee venom on Propionibacterium acnes-induced inflammatory skin disease in an animal model. Int. J. Mol. Med., 34: 1341-1348.

[1]www.kinetabio.com/autoimmunediseases.html

Ariesaadia, G., S. Sofer, E. Zlotkin and A. Shainberg, 1996. Effect of *Leiurus-quinquestriatus hebreus* venom on calcium and deoxyglucose uptake in cultured cardiac-cells. Toxicon, 34:435-442.

Ayres, R., P.R. Feijo, A.C. Cintra, M.A. Tomaz, P.A. Melo, V.M. Cunha and L.E.M. Quintas, 2015. Different effects of myotoxins bothropstoxin-I and II from *Bothrops* snake venom on cation transport ATPases from murine fast twitch skeletal muscle. Toxicon, 103: 80-84.

Beeton, C., M.W. Pennington and R.S. Norton, 2011. Analogs of the sea anemone potassium channel blocker ShK for the treatment of autoimmune diseases. Allergy Drug Targets, 10: 313-321.

Bernheimer, A.W., L.S. Avigad and C.Y. Lai, 1982. Purification and properties of a toxin from the sea anemone *Condylactis gigantea*. Arch. Biochem. Biophys., 214: 840-845.

Bhattacharya, S., P. Ghosh, T. De, A. Gomes, A. Gomes and S.R. Dungdung, 2013. *In vivo* and *in vitro* antileishmanial activity of *Bungarus caeruleus* snake venom through alteration of immunomodulatory activity. Exp. Parasitol., 135: 126-133.

Blankley, C.J., 1985. Chronicals of drug discovery, vol. 2. Edited by Jasjit S. Bindra and Daniel Lednicer. John Wiley and Sons, 605 Third Avenue, New York, NY 10158. 1983. 272 pp. 16×23.5 cm. ISBN 0-471-89135-5. $;44.95. J. Pharmaceut. Sci., 74: 1029-1030.

Bohlen, C.J. and D. Julius, 2012. Receptor-targeting mechanisms of pain-causing toxins: How ow? Toxicon, 60: 254-264.

Borchani, L., A. Sassi, H.B. Gharsa, I. Safra, D. Shahbazzadeh, Z.B. Lasfar and M. El Ayeb, 2013. The pathological effects of Heminecrolysin, a dermonecrotic toxin from *Hemiscorpius lepturus* scorpion venom are mediated through its lysophospholipase D activity. Toxicon, 68: 30-39.

Brubacher, J.R., D. Lachmanen, P.R. Ravikumar and R.S. Hoffman, 1999. Efficacy of digoxin specific Fab fragments (Digibind®) in the treatment of toad venom poisoning. Toxicon, 37: 931-942.

Caramalho, I., A. Melo, E. Pedro, M.M.P. Barbosa, R.M.M. Victorino, P. Santos and A.E. Sousa, 2015. Bee venom enhances the differentiation of human regulatory T cells. Allergy, 70: 1340-1345.

Casella-Martins, A., L.R. Ayres, S.M. Burin, F.R. Morais and J.C. Pereira *et al*., 2015. Immunomodulatory activity of *Tityus serrulatus* scorpion venom on human T lymphocytes. J. Venomous Anim. Toxins Includ. Trop. Dis., Vol. 21. 10.1186/s40409-015-0046-3

Chen, J.K., J. Capdevila and R.C. Harris, 2002. Heparin-binding EGF-like growth factor mediates the biological effects of P450 arachidonate epoxygenase metabolites in epithelial cells. Proc. Natl. Acad. Sci., 99: 6029-6034.

Clark, A.W., W.P. Hurlbut and A. Mauro, 1972. Changes in the finite structure of the neuro-muscular junction of the frog caused by black widow spider venom. J. Cell. Bio., 52: 1-14.

Correa-Netto, C., R. Teixeira-Araujo, A.S. Aguiar, A.R. Melgarejo and S.G. De-Simone *et al*., 2010. Immunome and venome of *Bothrops jararacussu*: A proteomic approach to study the molecular immunology of snake toxins. Toxicon, 55: 1222-1235.

Craig, A.G., T. Norberg, D. Griffin, C. Hoeger and M. Akhtar *et al*., 1999. Contulakin-G, an O-glycosylated invertebrate neurotensin. J. Bio. Chem., 274: 13752-13759.

Cruz, L.J., V. de Santos, G.C. Zafaralla, C.A. Ramilo, R. Zeikus, W.R. Gray and B.M. Olivera, 1987. Invertebrate vasopressin/oxytocin homologs. Characterization of peptides from *Conus geographus* and *Conus straitus* venoms. J. Biol. Chem., 262: 15821-15824.

Cruz, L.J., G. Kupryszewski, G.W. LeCheminant, W.R. Gray, B.M. Olivera and J. Rivier, 1989. Mu-Conotoxin GIIIA, a peptide ligand for muscle sodium channels: chemical synthesis, radiolabeling and receptor characterization. Biochemistry, 28: 3437-3442.

Cuypers, E., S. Peigneur, S. Debaveye, S. Kazuo and T. Jan, 2011. TRPV1 channel as new target for marine toxins: Example of gigantoxin I, a sea anemone toxin acting via modulation of the PLA_2 pathway. Acta Chim. Slov., 58: 735-741.

Debnath, P.K., G.N. Chaturvedi, S.K. Bhattacharya and Y.N. Upadhyaya, 1972. Comparative study of some pharmacological actions of crude and shodhita cobra venom. J. Res. Ind. Med., 7: 54-61.

Dixon, R.W. and J.B. Harris, 1996. Myotoxic activity of the toxic phospholipase, notexin, from the venom of the Australian tiger snake. J. Neuropathol. Exp. Neurol., 55: 1230-1237.

Doley, R. and R.M. Kini, 2009. Protein complexes in snake venom. Cell. Mol. Life Sci., 66: 2851-2871.

Dubovskii, P.V., A.A. Vassilevski, S.A. Kozlov, A.V. Feofanov, E.V. Grishin and R.G. Efremov, 2015. Latarcins: Versatile spider venom peptides. Cell. Mol. Life Sci., 72: 4501-4522.

Eddlestone, G.T., M. Komatsu, L. Shen and G.W. Sharp, 1995. Mastoparan increases the intracellular free calcium concentration in two insulin-secreting cell lines by inhibition of ATP-sensitive potassium channels. Mol. Pharmacol., 47: 787-797.

England, L.J., J. Imperial, R. Jacobsen, A.G. Craig and J. Gulyas *et al*., 1998. Inactivation of a serotonin-gated ion channel by a polypeptide toxin from marine snails. Science 281: 575-578.

Ericsson, C.D., C. Hatz, T. Junghanss and M. Bodio, 2006. Medically important venomous animals: Biology, prevention, first aid and clinical management. Clin. Infect. Dis., 43: 1309-1317.

Escoubas, P., J.R. De Weille, A. Lecoq, S. Diochot and R. Waldmann *et al*., 2000. Isolation of a tarantula toxin specific for a class of proton-gated Na^+ channels. J. Biol. Chem., 275: 25116-25121.

Farsky, S.H.P., L.R.C. Goncalves, J.M. Gutierrez, A.P. Correa, A. Rucavado, P. Gasque and D.V. Tambourgi, 2000. *Bothrops asper* snake venom and its metalloproteinase BaP-1 activate the complement system. Role in leucocyte recruitment. Mediators Inflamm., 9: 213-221.

Fialho, E.M.S., M.C.G. Maciel, A.C.B. Silva, A.S. Reis and A.K.M. Assuncao *et al*., 2011. Immune cells recruitment and activation by *Tityus serrulatus* scorpion venom. Toxicon, 58: 480-485.

Ford, P.M., W.R. Bell, R. Bluestone, J.M. Gumpel and F.W.S. Webb, 1970. The effect of Arvin on experimental immune arthritis in rabbits. Br. J. Exp. Pathol., 51: 81-86.

Gomes, A., P. Bhattacharjee, R. Mishra, A.K. Biswas and S.C. Dasgupta *et al*., 2010. Anticancer potential of animal venoms and toxins. Indian J. Exp. Biol., 48: 93-103.

Grattan-Smith, P.J., J.G. Morris, H.M. Johnston, C. Yiannikas, R. Malik, R. Russell and R.A. Ouvrier, 1997. Clinical and neurophysiological features of tick paralysis. Brain, 120: 1975-1987.

Grundemar, L. and E.D. Hogestatt, 1990. Vascular effects of helodermin, helospectin I and helospectin II: A comparison with vasoactive intestinal peptide (VIP). Br. J. Pharmacol., 99: 526-528.

Gupta, R.C., 2007. Veterinary Toxicology: Basic and Clinical Principles. 1st Edn., Elsevier, Amsterdam, pp: 777-810.

Hawgood, B.J., 1998. Hugh Alistair Reid OBE MD: Investigation and treatment of snake bite. Toxicon, 36: 431-446.

Herrera, C., T. Escalante, M.B. Voisin, A. Rucavado and D. Morazan *et al*., 2015. Tissue localization and extracellular matrix degradation by PI, PII and PIII snake venom metall oproteinases: Clues on the mechanisms of venom-induced hemorrhage. PLoS. Negl. Trop. Dis., Vol. 9. 10.1371/journal.pntd.0003731

Hodgson, W.C. and J.C. Wickramaratna, 2002. *In vitro* neuromuscular activity of snake venoms. Clin. Exp. Pharmacol. Physiol., 29: 807-814.

Jimenez, E.C., S. Donevan, C. Walker, L.M. Zhou and J. Nielsen *et al*., 2002. Conantokin-L, a new NMDA receptor antagonist: Determinants for anticonvulsant potency. Epilepsy Res., 51: 73-80.

Jo, M., M.H. Park, P.S. Kollipara, B.J. An and H.S. Song *et al*., 2012. Anti-cancer effect of bee venom toxin and melittin in ovarian cancer cells through induction of death receptors and inhibition of JAK2/STAT3 pathway. Toxicol. Applied Pharmacol., 258: 72-81.

Jover, E., F. Couraud and H. Rochat, 1980. Two types of scorpion neurotoxins characterized by their binding to two separate receptor sites on rat brain synaptosomes. Biochem. Biophys. Res. Commun., 95: 1607-1614.

Junghanss, T and M. Bodio, 1996. Notfall-Handbuch Gifttiere. Thieme Publishers, Stuttgart, Germany, ISBN-13: 9783131004413, Pages: 646.

Karalliedde, L., 1995. Animal toxins. Br. J. Anaes., 74: 319-327.

Kou, J.Q., R. Han, Y.L. Xu, X.L. Ding and S.Z. Wang *et al.* 2014. Differential effects of *Naja naja atra* venom on immune activity. Evidence-Based Complementary Altern. Med., 10.1155/2014/287631

Liu, Z.H., W. Qian, J. Li, Y. Zhang and S. Liang, 2009. Biochemical and pharmacological study of venom of the wolf spider *Lycosa singoriensis*. J. Venom Anim. Toxins Includ. Trop. Dis., 15: 79-92.

Livett, B.G., K.R. Gayler and Z. Khalil, 2004. Drugs from the sea: Conopeptides as potential therapeutics. Curr. Med. Chem., 11: 1715-1723.

Lu, D.L. and D.F. Zhang, 2001. Two kinds of poisonous spiders in Xinjiang and prevention and cure for the spider bite. Chin. J. Zool., 36: 40-42.

Luna, K.P.O., C.M.L. Melo, V.P. Pascoal, O.A. Martins-Filho and V.R.A. Pereira, 2011. *Bothrops erythromelas* snake venom induces a proinflammatory response in mice splenocytes. Int. J. Interferon Cytokine Mediators Res., 3: 9-18.

Markovic, O. and L. Rexova, 1963. The components of various types of honeybee venoms. Chem. Paper, 17: 676-684.

Matsunaga, S., N. Fusetani and S. Konosu, 1985. Bioactive marine metabolites, IV. Isolation and the amino acid composition of discodermin a, an antimicrobial peptide, from the marine sponge *Discodermia kiiensis*. J. Nat. Prod., 48: 236-241.

McCleskey, E.W., A.P. Fox, D.H. Feldman, L.J. Cruz, B.M. Olivera, R.W. Tsien and D. Yoshikami, 1987. Omega-conotoxin: Direct and persistent blockade of specific types of calcium channels in neurons but not muscle. Proc. Natl. Acad. Sci. USA., 84: 4327-4331.

McIntosh, J.M., A. Hasson, M.E. Spira, W.R. Gray and W. Li *et al*., 1995. A new family of conotoxins that blocks voltage-gated sodium channels. J. Biol. Chem., 270: 16796-16802.

Meves, H., 2008. Arachidonic acid and ion channels: An update. Br. J. Pharmacol., 155: 4-16.

Millers, E.K.I., M. Trabi, P.P. Masci, M.F. Lavin, J. de Jersey and L.W. Guddat, 2009. Crystal structure of textilinin-1, a Kunitz-type serine protease inhibitor from the venom of the Australian common brown snake (*Pseudonaja textilis*). FEBS J., 276: 3163-3175.

Moeller, H.B., T.S. Aroankins and R.A. Fenton, 2012. PP_1 and PP_{2a} phosphatases can modulate AQP_2 endocytosis. FASEB J., 10.1096/fj.1530-6860

Mohammadi, E., H. Vatanpour and F.H. Shirazi, 2015. Immunomodulatory effects of bee venom in human synovial fibroblast cell line. Iran J. Pharm. Res., 14: 313-320.

Morgenstern, D. and G.F. King, 2013. The venom optimization hypothesis revisited. Toxicon, 63: 120-128.

Myers, R.A., G.C. Zafaralla, W.R. Gray, J. Abbott, L.J. Cruz and B.M. Olivera, 1991. α-Conotoxins, small peptide probes of nicotinic acetylcholine receptors. Biochemistry, 30: 9370-9377.

Nipate, S., V.B. Soni and M.M. Ghaisas, 2014. Anti-arthritic effect of Indian red scorpion (Mesobuthustamulus) venom in freund's complete ad-juvant and collagen type II induced arthritis. J. Clin. Toxicol., Vol. 4. 10.4172/2161-0495.1000192

Nirthanan, S., E. Charpantier, P. Gopalakrishnakone, M.C.E. Gwee and H.E. Khoo *et al*., 2003. Neuromuscular effects of candoxin, a novel toxin from the venom of the Malayan krait (*Bungarus candidus*). Br. J. Pharmacol., 139: 832-844.

Norton, T.R., S. Shibata, M. Kashiwagi and J. Bentley, 1976. Isolation and characterization of the cardiotonic polypeptide anthopleurin-A from the sea anemone *Anthopleura xanthogrammica*. J. Pharm. Sci., 65: 1368-1374.

Olivera, B.M., J.M. McIntosh, L.J. Curz, F.A. Luque and W.R. Gray, 1984. Purification and sequence of a presynaptic peptide toxin from *Conus geographus* venom. Biochemistry, 23: 5087-5090.

Orsolic, N., 2012. Bee venom in cancer therapy. Cancer Metastasis Rev., 31: 173-194.

Pal, S.K., A. Gomes, S.C. Dasgupta and A. Gomes, 2002. Snake venom as therapeutic agents: From toxin to drug development. Indian J. Exp. Biol., 40: 1353-1358.

Petricevich, V.L., A.H. Cruz, F.I.V. Coronas and L.D. Possani, 2007. Toxin gamma from *Tityus serrulatus* scorpion venom plays an essential role in immunomodulation of macrophages. Toxicon, 50: 666-675.

Pu, X.C., P.T.H. Wong and P. Gopalakrishnakone, 1995. A novel analgesic toxin (hannalgesin) from the venom of king cobra (*Ophiophagus hannah*). Toxicon, 33: 1425-1431.

Rajagopalan, N., R.M. Kini, R. Doley and R.P. Hegde, 2009. Snake Venom Three Finger Toxins. In: Handbook of Venoms and Toxins of Reptiles, Mackessey, S.P. (Ed.). CPC Press, USA., pp: 287-301.

Raouraoua-Boukari, R., S. Sami-Merah, D. Hammoudi-Triki, M.F. Martin-Eauclaire and F. Laraba-Djebari, 2012. Immunomodulation of the inflammatory response induced by androctonus australis hector neurotoxins: Biomarker interactions. Neuroimmunomodulation, 19: 103-110.

Rashid, M.H., R. Huq, M.R. Tanner, S. Chhabra and K.K. Khoo *et al*., 2014. A potent and Kv1. 3-selective analogue of the scorpion toxin HsTX1 as a potential therapeutic for autoimmune diseases. Sci. Rep., Vol. 4. 10.1038/srep04509

Ribeiro, C.B., J.C. dos Santos, J.M. Silva, P.H.S. de Godoi and M.R. Magalhaes *et al*., 2014. *Crotalus durissus collilineatus* venom induces TNF-α and IL-10 production in human peripheral blood mononuclear cells. ISRN Inflammation. 10.1155/2014/563628

Rinehart, K.L., J.B. Gloer, J.C. Cook Jr., S.A. Mizsak and T.A. Scahill, 1981. Structures of the didemnins, antiviral and cytotoxic depsipeptides from a caribbean tunicate. J. Am. Chem. Soc., 103: 1857-1859.

Sampaio, S.C., S. Hyslop, M.R.M. Fontes, J. Prado-Franceschi and V.O. Zambelli *et al*., 2010. Crotoxin: Novel activities for a classic β-neurotoxin. Toxicon, 55: 1045-1060.

Santos Torres, J., M.A. Slimak, S. Auer and I. Ibanez Tallon, 2011. Cross-reactivity of acid-sensing ion channel and Na^+-H^+ exchanger antagonists with nicotinic acetylcholine receptors. J. Physiol., 589: 5109-5123.

Schieck, A., F. Kornalik and E. Habermann, 1972. The prothrombin-activating principle from *Echis carinatus* venom. I. Preparation and biochemical properties. Naunyn-Schmiedeberg's Arch. Pharmacol., 272: 402-416.

Shon, K.J., A. Hasson, M.E. Spira, L.J. Cruz, W.R. Gray and B.M. Olivera, 1994. Delta-Conotoxin GmVIA, a novel peptide from the venom of *Conus gloriamaris*. Biochemistry, 33: 11420-11425.

Soroceanu, L., Y. Gillespie, M.B. Khazaeli and H. Sontheimer, 1998. Use of chlorotoxin for targeting of primary brain tumors. Cancer Res., 58: 4871-4879.

Sribar, J., A. Copic, M. Poljsak-Prijatelj, J. Kuret, U. Logonder, F. Gubensek and I. Krizaj, 2003. R25 is an intracellular membrane receptor for a snake venom secretory phospholipase A_2. FEBS Lett., 553: 309-314.

Stair, E.L. and K.H. Plumlee, 2004. Blister Beetles. In: Clinical Veterinary Toxicology, Plumlee, K.H. (Ed.). Mosby, St. Louis, MO., pp: 101-103.

Teixeira, C., Y. Cury, V. Moreira, G. Picolo and F. Chaves, 2009. Inflammation induced by *Bothrops asper* venom. Toxicon, 54: 67-76.

Teixeira, C.F.P., E.C.T. Landucci, E. Antunes, M. Chacur and Y. Cury, 2003. Inflammatory effects of snake venom myotoxic phospholipases A_2. Toxicon, 42: 947-962.

Teixeira, C.F.P., C.M. Fernandes, J.P. Zuliani and S.F. Zamuner, 2005. Inflammatory effects of snake venom metalloproteinases. Memorias do Instituto Oswaldo Cruz, 100: 181-184.

Tu, A.T., 1974. Sea snake venoms and neurotoxins. J. Agric. Food Chem., 22: 36-43.

WHO., 2015. Neglected Tropical Diseases Snakebite. World Health Organization, Rome, Italy.

Warrell, D.A., 2003. Injuries, Envenoming, Poisoning and Allergic Reactions Caused by Animals. In: Oxford Textbook of Medicine, Warrell, D.A., T.M. Cox and J.D. Firth (Eds.). 4th Edn., Vol. 1, Oxford University Press, Oxford, UK., ISBN-13: 9780198570141, pp: 923-946.

Wasserman, S.I., 1983. Mediators of immediate hypersensitivity. J. Aller. Clin. Immunol., 72: 101-115.

Wigger, E., L. Kuhn-Nentwig and W. Nentwig, 2002. The venom optimisation hypothesis: A spider injects large venom quantities only into difficult prey types. Toxicon, 40: 749-752.

Wulff, H. and B.S. Zhorov, 2008. K^+ channel modulators for the treatment of neurological disorders and autoimmune diseases. Chem. Rev., 108: 1744-1773.

Yan, L. and M.E. Adams, 1998. Lycotoxins, antimicrobial peptides from venom of the wolf spider *Lycosa carolinensis*. J. Biol. Chem., 273: 2059-2066.

Yang, S. and G. Carrasquer, 1997. Effect of melittin on ion transport across cell membranes. Zhongguo Yao Li Xue Bao, 18: 3-5.

Yeh, C.H., H.C. Peng, R.S. Yang and T.F. Huang, 2001. Rhodostomin, a snake venom disintegrin, inhibits angiogenesis elicited by basic fibroblast growth factor and suppresses tumor growth by a selective α_v β_3 blockade of endothelial cells. Mol. Pharmacol., 59: 1333-1342.

Zhao, Y., J. Huang, X. Yuan, B. Peng, W. Liu, S. Han and X. He, 2015. Toxins targeting the KV1.3 channel: Potential immunomodulators for autoimmune diseases. Toxins, 7: 1749-1764.

Zingali, R.B., H.C. Castro, R.Q. Monterio, M. Assafirm and C. Bon, 2006. Structural and pharmacological studies of bothrojaracin or (pro) thrombin action. Proceedings of the 15th World Congress of Animal, Plant and Microbial, Toxins, July 23-28, 2006, Glasgow, Scotland.

Zoccal, K.F., C.S. Bitencourt, A. Secatto, C.A. Sorgi and K.C.F. Bordon *et al*., 2011. *Tityus serrulatus* venom and toxins Ts1, Ts2 and Ts6 induce macrophage activation and production of immune mediators. Toxicon, 57: 1101-1108.

Zoccal, K.F., C. da Silva Bitencourt, C.A. Sorgi, K. de Castro Figueiredo Bordon, S.V. Sampaio, E.C. Arantes and L.H. Faccioli, 2013. Ts6 and Ts2 from *Tityus serrulatus* venom induce inflammation by mechanisms dependent on lipid mediators and cytokine production. Toxicon, 61: 1-10.