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Review Article

Pharmacological Activities of Clinically Relevant Venoms and Specific Venom-derived Drugs Approved for use in Medicine

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ABSTRACT

Venoms are generally aqueous solutions with cocktail of complex mixture of components mainly proteins and peptide toxins with pathophysiological functions. Venomous animals produced toxins in a bid to live favorably in a particular environment or in order to win among animals. As a consequence, animal envenoming's, notably following bite or sting by snake, scorpion and spider precipitate life-threatening pathological conditions. Evidence suggests that evolutional events endowed each venom toxin with unique, thereby enabling the bioactive compound to act on molecular targets with high affinity, potency, specificity and selectivity. The aforementioned properties of venom toxins, which are often not found in natural or synthetic small molecules, make them valuable resource for development of pharmacological interventions. This review provides an overview of medically most important snake, scorpion and spider toxins as well as their molecular targets and biological activities. Specific venom-derived drugs that have been successfully translated into human therapeutics are discussed as well.

Keywords: Bioactive; Drugs; Evolutional event; Pathophysiological changes; Therapeutics; Toxins; Venoms

INTRODUCTION

Myriad of venomous animals have been identified and are widely spread throughout the world. Many of these animals developed a specialized gland for producing venom and wounding apparatus for delivering the venom, which consists of toxins that disrupt physiological and biochemical processes so as to facilitate feeding on prey or defence against predators and rivals [1-3]. Of note, venomous animals without delivery apparatus including but not limited to amphibians, bufferfish have glands located in various skin sites [4]. Compounds used as venoms in animals are the result of evolutional events, involving recruitment of protein genes fined-tuned to obtain multi-gene families, which preserved the molecular scaffolds of ancestral proteins, but with unique surface functional residues [3]. It is well documented that several variety of toxins may be present in a single venom, acting in synergetic fashion to produce pathophysiological changes, an important strategy to reduce amount of venom dispensed given the high metabolic cost of venom production [5,6].

In essence, venoms are aqueous solutions with cocktail of complex mixture of components mainly proteins (with or without enzymatic properties) and small molecule peptides, although the composition varies between and within species, a function of animals' geographical location, habitant and age [7-10]. Of venomous animal studied, snake, scorpion and spider envenomings through bite or sting are considered medically most relevant owing to significant morbidity, disability or mortality associated with their envenoming. For instance, snake venoms have variable toxin components as compared to venoms from other animals. The pathophysiological changes associated with scorpion and spider envenomings are caused mainly by dipeptide toxins, whereas snake venoms consist of more diverse array of larger proteins and peptide toxins, which underpin wider spectrum of effects observed in the victims of snake envenomings [11,12]. Other components (non-protein compounds) of venoms with less pathological effects include polyccharides, lipids, salts, nucleosides, nucleotides, riboflavin, serotonin and histamine [4,10].

Delineation of pathophysiological mechanisms of animal envenomings have led to discovery of many pharmacological

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targets such as G protein-coupled receptors, ion channels and membrane transporters. This is due to the fact that the evolutional events endowed each venom toxin with unique "molecular fingerprint", thereby enabling the bioactive compound to act on molecular targets with high affinity, potency, specificity (distinction among receptor types) and selectivity (distinction among receptor subtypes) [6,8,13,14]. Hence, venom toxins are brilliant pharmacological tools and drug candidates. This review provides valuable insights into clinically most important snake, scorpion and spider toxins as well as their molecular targets and biological activities. Additionally, the paper discusses specific venom-based drugs that have successfully progressed to market.

SNAKE VENOM TOXIN FAMILIES

Notwithstanding wide variety of snake toxin components, the clinically most relevant and commonly explored toxin families include three finger toxins, phospholipases A_2, snake venom metalloproteinases and snake venom serine proteinases.

Three finger toxins

Three finger toxins (3FTXs) are non-enzymatic proteins found in the venom of elapid and colubrid snakes. They are characterized by 57 to 85 amino acid residues, with a shared common scaffold of three β-stranded loops protruding from central hydrophobic core, stabilized by 4 to 5 conserved disulphide bond [15,16]. Despite the common structural orientation, they interact with different molecular targets to exert wide range of effects, a function of subtle variation in the position of the disulphide bond, amino acid residues and length of their loops [6,16]. Thus, 3FTXs are classified as neurotoxins, fasciculins, cardiotoxins, calcipine and FS_2, mambalgins and dentroaspin based on their distinctly functional bioactivity.

Neurotoxins, including α-neutoxins, κ-neurotoxins and muscarinic toxins reversibly block muscle nicotinic acetylcholine receptors (nAChRs), neuronal nAChRs and muscarinic receptors respectively to bring about spastic paralysis [16,17]. Fasciculins inhibit acetylcholinesterase (AChE), leading to ACh accumulation at the synapse with eventual flaccid paralysis [11,17]. Cardiotoxins (cytotoxins) bind avirdly to membrane phospholipids, disrupt membrane permeability to induce necrosis [11,17]. Another group of cardiotoxins known as β-cardiotoxins block β-adrenoceptors to slow the heart rate [15,17]. Calcipine and FS_2 block L-type of calcium channel, resulting to the impediment of calcium current with consequent decrease in the heart rate [17]. Mambalgins inhibit acid sensing ion channels (ASICs), a such exert analgestic effect strong as morphine, but without likelihood of addiction. Dendroaspin (mambin) interferes with the interaction between fibrinogen and its receptors, the glycoprotein IIb/IIIa, thereby inhibiting platelet aggregation with eventual alteration of haemostasis [11,15].

Phospholipases A^2

Phospholipases A_2 (PLA_2s) are conventionally recognized to be four groups (I, II, III and IV). Group I and II are major components in the venom of *Elapidae* and *Viperidae* families respectively [10,18]. These hydrolytic enzymes are basically cysteine rich proteins with 119 to 134 amino acid residues, stabilized by seven disulphide bridges [16,18]. They share similar structures and functions, particularly calcium dependent catalytic mechanism, however, group I and II mainly differed due to differences in the pattern of disulphide bond, presence or absence of N-terminal heptapeptide and solitary half cysteine [18]. PLA_2s trigger a wide variety of toxic activities that are either dependent or independent of their catalytic activity. Mytotoxic and neurotoxic PLA_2s are described. Both mytotoxins and neurotoxins perturb plasma membrane of skeletal muscle cells and motor nerve terminal, alter structural integrity of the bilayer membrane to induce an increased ions permeability, more importantly Ca^{2+} with eventual cytosolic Ca^{2+} overload, which often lead to severe degenerative events, including but not limited to necrosis [19,20]. Most neurotoxic PLA_2s bind to presynaptic membrane of motor nerve terminal and terminal part of motor axon, causing neuromuscular paralysis [16,19]. Other effects precipitated by both toxins include proinflammatory, oedemic, anticoagulant, haemolytic and bactericidal effects.

SNAKE VENOM METALLOPROTEINASES

Snake Venom Metalloproteinases (SVMPs) are Zn^{2+} dependent proteolyte enzymes and are classified as P-I, P-II and P-III, according to their domain configuration, with molecular masses of 20-30 kDa, 30-60 kDa and 60-100 kDa respectively [7,21]. While Zn^{2+} is required for catalytic activity of SVMPs, Ca^{2+} provides structural stability. These toxins are major components in the veperid venoms, although P-III SVMPs are abundant in colubrid venoms and relatively low in elipid venoms [11,16]. The abundance differences partly explain why the victims of various species envenomings are presented with distinct pathologies. SVMPs indirectly induce haemorrhage by binding and hydrolyzing structural components such as type IV collgen in the basement membrane of capillary blood vessels and adhension proteins of endothelial cell matrix [11,12]. This cleavage of cell-cell junction weakens the scaffold structure and haemodynamic forces, leading to disruption of capillary wall and eventual marked extravasation of blood [10,22].

Furthermore, some SVMPs, especially P-I SVMPs with a single proteinase domain exert fibrinolytic effects, which enhance haemorrhage. They cleave both α and β chains of fibrinogen and degrade them independent of activation of plasminogen [11,22]. This ultimately results in defibrination with a consequence bleeding disorder. The haemorrhagic condition is exacerbated by activities of disintegrins, a non-enzymatic domain of SVMPs. These proteins bind to glycoprotein IIb/IIIa receptor (integrin) on activated platelets, thus preventing fibrinogen from binding to platelets, thereby inhibiting platelet aggregation [10,12]. In addition, SVMPs induce inflammation, pain and dermonecrosis.

SNAKE VENOM SERINE PROTEINASES

Snake Venom Serine Proteinases (SVSPs) are proteolytic enzymes found in several snake families. However, they are typically abundant in viper venoms and relatively low in the venoms of elapid and colubrid snakes. The molecular masses of SVSPs range from 26 kDa to 67 kDa, depending on the extent of glycosylation [11]. The multifunctional enzymes generally affect haemostatic system. Some SVSPs known as Thrombin-Like Enzymes (TLEs) exhibit selective functionality. Most TLEs mainly act on α chain of fibrinogen, although some only cleave the β chain and a few target both α and β chains. This cleavage leads to conversion of fibrinogen into fibrin [12]. Since SVSPs generally do not activate coagulation factor XIII to cross-linked the fibrin, the unstable clot form is readily dispersed by plasmin, hence, contributing to establishment of coagulopathy [11,12]. Another anticoagulation activity of these toxins is activation of protein C, which inhibits coagulant factors Va and VIIIa. In contrast, procoagulant SVMPs act on important elements of coagulation cascade to activate clotting factors such as V, IX, X and prothrobin.

Apart from SVMPs and SVSPs, there are other snake toxin components that play a key role in perturbation of haemostasis. For instance, Bradykenin Potenting Peptides (BPPs) isolated from numerious viper species inhibit Angiotensin Converting Enzyme (ACE), thereby preventing conversion of angiotensin I into angiotensin II, resulting to decrease in systemic vascular resistance [12]. This haemodynamic effect is enhanced by SVMPs and SVSPs that activate plasma kininogen, the effect associated with hypotension observed following envenoming.

SCORPION VENOM TOXINS

Scorpion venoms contain several toxins, mostly small peptide toxins that may interact with one another to modulate the activities of neuronal ion channels, including Ca^{2+}, Na^{+}, K^{+} and Cl^{-} channels [23]. Of most clinically important are α and β toxins, which consist of 61 to 76 amino acid residues, cross-linked by four disulphide bridges [23,24]. These neurotoxins have essential three-dimensional structure, highly conserved comprising α-helix and three or four-stranded anti-parallel β-sheets with high chemical and thermal stability [23]. The α-neurotoxins bind with high affinity to the resting state of voltage gated sodium (Nav) channels and inhibit fast inactivation by interacting with channel receptor site 3 with resultant prolong depolarization [23-25]. On the other hand, β-toxins target neurotoxin receptor site 4 to cause sub-threshold channel opening by shifting the Nav channel activation towards a more negative membrane potential [23,25]. Ultimately, Nav channel specific toxins bring about autonomic excitation (both sympathetic and parasympathetic) with eventual marked systemic effects [24]. The combination of sympathetic excitation and subsequent release of catecholamines cause tachycardia, myocardial injury, pulmonary oedema and cardiogenic shock [24,26]. In contrast to sympathetic effects, parasympathetic effects are less severe and can cause short-lived increased cholinergic tone with associated copious tracheo-bronchial secretion, salivation, lacrimation, sweating, involuntary defecation, urination and priapism [26].

SPIDER VENOM TOXINS

The majority of envenoming cases involving spider bites cause minor effects. However, spider toxin components of genera Latrodectus, Loxoscele, Phoneutria and Atrax were reported to cause lethal effects, therefore are medically important [27].

α-Latrotoxin

α-Latrotoxin (α-LTX) is a non-enzymatic protein of about 130 kDa found in the venom of black widow spider (*Latrodectus* spp.) [28]. α-LTX selectively binds to presynaptic neuronal membrane to exert its effects via: (i) Ca^{2+} dependent action, mediated through neurexin receptors, involving toxin aggregation into homotetrametic complexes, which are inserted into lipid bi-layer membrane to create a channel-like pore that persistently open. The pore permits influx of small molecules and cations including but not limited to Ca^{2+} from extracellular domain. (ii) Ca^{2+} independent action, which involves letrophilin, a G protein-coupled receptor that triggers cascade of events with eventual release of Ca^{2+} from extracellular stores [28-30]. Ultimately, these actions cause strong and sustained exocytosis of all known neurotransmitters from presynaptic cells, resulting to blockade of signal transmission [29]. This outcome is associated with latrodectism that is clinically manifested as generalized muscle pain, diaphoresis, cramps, vomiting and chills [31]. In severe cases, the victim may be presented with myocardial infarction and compartment syndrome.

Sphingomyelinases D

Sphingomyelinases D (SMases) are the main toxins in the venom of brown spider (Loxoscele spp.). SMases also known as phospholipases D, are low molecular mass proteins (31 to 35 kDa). These enzymes directly target lipid bi-layer membrane to induce hydrolysis of sphingomyelin, resulting to the formation of ceramide with potency to activate cascade of reactions, including components of complement system, migration of polymorphonuclear leukocytes, platelet aggregation and inflammation response [27,31]. These events bring about loxosclitism, clinically manifested as skin necrosis at site of bite with gravitational lesion spreading, while systemic envenoming is presented as intravascular haemolysis, thrombocytopenia, distributed intravascular coagulation and acute renal failure.

PnTx2-5 and PnTx2-6

These are neurotoxins with low molecular mass proteins (3.5 to 9 kDa) found in the venom of *Phoneutria nigriventer* spider. They bind to Na_v channels and alter channel kinetics, resulting to inhibition of fast inactivation and a shift in the voltage dependent activation and steady-state inactivation towards a hyperpolarized membrane potential [32]. At cellular level, both toxins exert similar effects on the Nav channel kinetics, but in neuronal Na_v channels, PnTx2-6 exhibits higher affinity with more proclivity for delaying fast inactivation and shifting the steady-state inactivation than PnTx2-5 [32]. Addition to activation of Nav described above, the neurotoxins block Ca_v and K_v channels in the muscle fibers and neuronal cells to produce autonomic excitation (both sympathetic and

parasympathetic). Consequently, neurotransmitters are discharged, chiefly catecholamines and acetylcholine, which explains why the victims of *P nigriventer* spider bite are presented with plethora of morbid conditions and may be manifested as local pain followed by profuse sweating, copious salivation, lacrimation, nausea, vomiting, tachycardia, tremor, muscle spasm and priapism.

ANIMAL TOXINS AS A SOURCE OF THERAPEUTIC AGENTS

Evolutional events endowed venom proteins with characteristics that enable them to act on molecular targets with high affinity, potency, specificity and selectivity. The above properties of venom toxins, which are often not found in natural or synthetic small molecules make them more amenable for use as compound leads, templates on which further optimization can be performed with a view to providing novel pharmacological interventions [33]. A growing body of research suggests that animal toxins are promising therapeutic tools for management of plethora of clinical conditions, including cancer, pain, cardiovascular disorders as well as metabolic, infectious and various neurodegenerative diseases [5,8,34,35]. In principle, therapeutic applications of animal toxins demonstrate how a patient's source of toxicity may become another patient's source of therapy. So far, paucity of venom toxins has successfully progressed to clinic. Specific venom-based drugs licensed by regulatory agent for use in medicine are summarized in the following paragraphs.

Identification of bradykinin potentiating peptides (BPPs) in snake venoms by Prof Sergo Ferreira was acknowledged as a quantum leap in annals of medicine. This peptide inhibits the conversion of angiotensin I into angiotensin II as well as degradation of bradykinin, thereby decreasing systemic vascular resistance [12]. Consequently, Captopril, a synthetic analoque of BPP isolated from the venom of Brazilian pit viper (*Bathrops jaracaca*) was subsequently developed [12,36]. Clinically, the drug is indicated in hypertension, congestive heart failure and myocardial infarction and type I diabetic nephropathy.

Glycoprotein (GP) IIb/IIIa is an adhensive receptor involved in platelets aggregation. Disintegrins found in certain snake venoms are GP IIb/IIIa antagonists, thus prevent the aggregation of platelets. Synthetic analogues of disintegrins such as Eptifibatide (Integrilin®), a cyclic heptatide and Tirofiban (Aggrastat®), a non-peptide were derived from the venom of saw-scaled viper (*Echis carinatus*) and pygmy rattlesnake (*Sistrurus miliarius* barbouri) respectively [12,37]. These two antithrobiotic/anticoagulant drugs are indicated in unstable angina and acute coronary syndrome. They also have a place in surgical intervention e.g. angioplasty procedure.

DISCUSSION

Batroxobin (Defibrase®) is a drug isolated from the venom of the Brazilian lancehead viper (*Bathrops moojeni*). As with certain snake venom, serine proteinases (SVSPs) described as thrombi like enzymes (TLEs), Batroxobin initially promote the formation of clot that is unstable, thus the clot is readily dissolved by plasmin [12]. Due to this anticoagulation effect, the drug is indicated for the treatment of ischaemic stroke, myocardial and cerebral infarctions and wound management after surgical procedures.

Bivalirudin (Angiomas®) is a synthetic analogue of hirudin, a peptide toxin obtained from *Hirudo medicinalis* (medicinal leech). Literature data testify that bivalirudin has salutary anticoagulation effect. Unlike heparin, bivalirudin directly inhibit both free and bound thrombin, a feature that has made it anticoagulant of choice in certain cardiovascular events [38,39]. It was approved for use as an anticoagulant in adults with unstable angina undergoing percutaneous transluminal coronary angioplasty. Other indications include percutaneous coronary intervention with provisional use of glycoprotein IIb/IIIa therapy and individuals with or at risk of heparin-induced thrombocytopenia and/or thrombosis syndrome [39].

Omega-conotoxin MVII A, a 25 amino acid residue peptide isolated from marine cone snail (*Conus magus*) selectively blocks N-type of calcium ion (Cav 2.2) channels, which is involved in pain signalling in the dorsal horn of the spinal cord [40,41]. This peptide progressed through clinical trials and was renamed Ziconotide (Priait®), a non-narcotic analgesic approved, especially for treatment of protracted pain when there is poor clinical outcomes after application of other medications indicated for the condition [36].

Glucagon like peptide 1 (GLP 1) is an incretin hormone, which exerts antidiabetic effect, though with very short plasma half-life (1.5-2 hours) due to rapid degradation by dipeptidyl peptidase-4 (DPP-4) [36,42]. Exenatide® is an incretin hormone analogue derived from exentin-4 peptide in the venom of Gila monster (*Heloderma suspectum*) [43]. It is more resistance to enzymatic degradation by DPP-4, thus has longer half-life (about 2.4 hours) than native GLP 1 [36,42,43]. The drug is approved as injectable, adjunct therapy in patients with type 2 diabetes treated with metformin or sulfonylureas that still have suboptimal glycemic control.

CONCLUSION

Venomous animals produced toxins in a bid to live favourably in a particular environment or in order to win "arms race" among animals. As a consequence, animal envenomings, notably following bite or sting by snake, scorpion and spider precipitate life-threatening morbid conditions. Paradoxically, owing to their unique pharmacological properties, the animal toxins have become source of medical interventions, which prolong and enhance human existence. This illustrates how one patient's source of toxicity may become another patient's source of therapy. The specific venom-derived medications discussed in this paper are the representatives of success stories of animal toxins translated into human therapeutics. Even more exciting, however, are several promising molecules, which are still clinical candidates or in various stages of preclinical development.

REFERENCES

1. Maijden A, Kosh B, Valk, T, Vergas-Munoz, LJ, Estrada-Gomez S. Target specificity in scorpions: Comparing lethality of scorpion venoms across arthropods and vertebrates. Toxins. 2017;9(10):312.
2. Zhang Y. Why do we study animal toxins? Zoological Research. 2015;36(4):183-222.
3. Fry BG, Roelants K, Champagne DE, Scheib H, Tyndall JD, King GF, et al. The toxicogenomic multiverse: Convergent recruitment of proteins into animal venoms. Annu Rev Genomics Hum Genet. 2009;10(1):483-511.
4. Utkin YN. Animal venom studies: Current benefits future developments. World J Biol Chem. 2015;6(2):28-33.
5. de Souza JM, Goncalves BDC, Gomez MV, Vieira LB, Riberiro FM. Animal toxins as a therapeutic tools to treat neurodegenerative diseases. Front Pharmacol. 2018;9(1):1-25.
6. Nirthanan S, Gwee M. Three finger α-neurotoxins and nicotinic acetycholine receptor, forty years on. J Pharmacol Sci. 2004;94(1):1-7.
7. El-Aziz TM, Soares AG, Stockand JD. Snake venoms in drug discovery: Valuable therapeutic tools for life saving. Toxins. 2019;11(10):564.
8. Chen N, Xu S, Zhang Y, Wang F. Animal protein toxins: Origins and therapeutic implications. Biophys Rep. 2018;4(5):233-242.
9. Sani I, Umar RA, Hassan SW, Faruq, U. Antisnake venoms and their mechanisms of action: A review. Saudi J Med Pharm Sci. 2018;4(5):512-520.
10. Fatima L, Fatah C. Pathophysiological and pharmacological effects of snake venom components: molecular targets. J Clin Toxicol. 2014;4(2):190.
11. Ferraz CR, Arrahman A, Xie, C, Casewell NR, Lewis RJ, Kool J, et al. Multifunctional toxins in snake venom therapeutic implications: From pain to hemorrhage and necrosis. Front Ecol Evol. 2019;7(9):1-19.
12. Slagboon J, Kool J, Harrison RA, Casewell NR. Haemotoxic snake venoms: Their functional activity, impact on snake bite victims and pharmaceutical promise. Br J Haematol. 2017;177(6):947-959.
13. Takacs Z, Nathan S (2014) Animal venoms in medicine. Encyclopedia of Toxicology. 2014;1(5):252-259.
14. Jungo F, Estreicher A, Bairoch A, Bouguelect I, Xenarios L. Animal toxins: How complexity represented in databases? Toxins. 2010;2(2): 262-282.
15. Utkin YN. Last decade update for three finger toxins: Newly emerging structure and biological activities. World J Biol Chem. 2019;10(1): 17-27.
16. Bermudez-Mendez E, Fulgsang-Madsen A, Fons S, Lemonte B, Gutierrez JM, Lausten AH. Innovative immunization strategies for antivenom development. Toxins. 2018;10(11):452.
17. Munawar A, Ali S, Akrem A, Betzel C. Snake venom peptides: Tools for biodiscovery. Toxins. 2018;10(11):474.
18. Samy PR, Gopalakrishnakone P, Stile BG, Girish KS, Swamy SN, Hemshekhar M, et al. Snake venom phospholipase A2: A novel tool against bacterial disease. Curr Med Chem. 2012;19(36):6150-6162.
19. Harris JB, Scott-Davey T. Secreted phospholipases A2 of snake venoms: Effects on the peripheral neuromuscular system with comments on the role of phospholipase A2 in disorders of the CNS and their use in industry. Toxins. 2013;5(12):2533-2571.
20. Montecucco C, Gutierrez JM, Lomonte B. Cellular pathology induced by snake venom phospholipase A2 myotoxins and neurotoxins: Common aspect of their mechanisms of action. Cell Mol Life Sci. 2008;65(18):2897-2912.
21. Gasanov SE, Dagda LK, Rael ED. Snake venom cytotoxins, phospholipase A2s and Zn2+-dependent metalloproteinases: Mechanisms of action and pharmacological relevance. J Clin Toxicol. 2014;4(1):181.
22. Gutierrez JM, Escalante T, Rucavado A, Herrera C. Haemorrhage caused by snake venom metalloproteinases: A journey of discovery and understanding. Toxins. 2016;8(4):93.
23. Quintero-Hernandez V, Jimenez-Vargas JM, Gurolla GB, Valdivia HH, Possani LD. Scorpion venom components that affect ion-channels function. Toxicon. 2013;15(76):328-342.
24. Isbister JK, Bawaskar HS. Scorpion envenomation. N Engl J Med. 2014;371(14):457-463.
25. Gilchrist J, Olivera BM, Bosmans F. Animal toxins influence voltage-gated sodium channel function. Handb Exp Pharmacol. 2014;221(1): 203-229.
26. Escalona MP, Possani LD. Scorpion beta-toxins and voltage-gated sodium channels: Interactions and effects. Front Biosci (Landmark Ed). 2013;18(1):572-587.
27. Sannaningaiah D, Subbaiah GK, Kempaiah K. Pharmacology of spider venom toxins. Toxin Reviews. 2014;33(4):206-220.
28. Ushkaryov YA, Rohou A, Sugita S. α–Lactrotoxin and its receptors. Handb Exp Pharmacol. 2008;184(1):171-206.
29. Langenegger N, Nentwig W, Kuhn-Nenwig, L. Spider venom: Components, modes of action and novel strategies in transcriptomic and proteinomic analyses. Toxins. 2019;11(10):611.
30. Yan S, Wang X. Recent advances in research on widow spider venoms and toxins. Toxins. 2015;7(12):5055-5067.
31. Cordeiro FA, Amorim FG, Anjolette FA, Arantis EC. Arachnid of medical importance in Brazil: main active components present in spider and scorpion venoms and tics saliva. J Venom Anim Toxins Incl Trop Dis. 2015;21(24):24.
32. de Lima ME, Figueiredo SG, Matavel A, Nunes KP, da Silva CN, Almeida FM, et al. Phoneutria nigriventer venom and toxins: A Review. Toxinology. Springer, Dordrecht. 2015.
33. Peignuer S, Tytgat J. Toxins in drug discovery and pharmacology. Toxins. 2018;10(3):126.
34. Shah P, Ali F, Qayyun S, Ahmed S, Haleem KS, Tauseef I. Scorpion venom: A poison or a medicine-minireview. Indian J Mar Sci. 2018;47(4):773-778.
35. Attarde SS, Pandit SV. Scorpion venom as therapeutic agent-current perspective. Int J Curr Pharm Rev Res. 2016;7(2):59-72.
36. Pennington MW, Czerwinski A, Norton RS. Peptide therapeutics from venom: Current status and potential. Bioorganic and Medical Chemistry. 2018;26(10):2738-2758.
37. Ojeda PG, Ramirez D, Alzate-Morale J, Caballero J, Kaas Q, Gonzalez W. Computational studies of snake venom toxins. Toxins. 2018;10(1): 8.
38. Jariwada P, Chandara KS. Bivalirudin: The relevance in today's interventional practice. Indian Heart Journal. 2012;64(5):449-452.
39. Warkentin JE, Greinader A, Koster A. Bivalirudin. Thromb Haemost. 2008;99(11):830-839.
40. Ramirez D, Gonzalez W, Fissore RA, Carvaxho I. Conotoxins as tools to understand the physiological function of voltage-gated calcium (Cav) channels. Mar Drugs. 2017;15(10):313.
41. Hannon HE, Atchison WD. Omega-conotoxins as experimental tools and therapeutics in pain management. Mar Drugs. 2013;11(3): 680-699.
42. Ahren B. Exenatide: A novel treatment of Type 2 diabetes. Therapy. 2005;2(2):207-222.
43. Sturla SJ, Boobis AR, FitzGerald RE, Hoeng J, Kavlock RJ, Schirmer K, et al. Systems toxicology: from basic research to risk assessment. Chem Res Toxicol. 2014;27(3):314-329.