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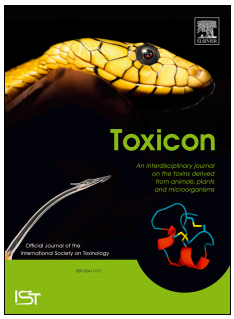

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Immune drug discovery from venoms

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Key words: venom, toxin, therapeutic, immune modulation, immune system

Abstract

This review catalogues recent advances in knowledge on venoms as standalone therapeutic agents or as blueprints for drug design, with an emphasis on venom-derived compounds that affects the immune system. We discuss venoms and venom-derived compounds that affect total immune cell numbers, immune cell proliferation, immune cell migration, immune cell phenotype and cytokine secretion. Identifying novel compounds that 'tune' the system, up-regulating the immune response during infectious disease and cancer and down-regulating the immune response during autoimmunity, will greatly expand the tool kit of human immunotherapeutics. Targeting these pathways may also open therapeutic options that alleviate symptoms of envenomation. Finally, combining recent advances in venomics with progress in low cost, high-throughput screening platforms will no doubt yield hundreds of prototype immune modulating compounds in the coming years.

Highlights

- Up to date review of venom and venom-derived compounds involved in immune modulation.
- Catalog of FDA approved venom-derived therapeutics.
- Mechanisms of immune modulation by snake, scorpion, bee and sea anemone secretions.
- Avenues for future translation of venom-derived immune modulators.

1. Introduction

There are approximately 8.7 million different species on Earth, (Mora et al., 2011) many of which produce venoms that have been refined over 600 million years of evolution for optimal potency and selectivity (Mauri et al., 2017). Animal venoms have been used to treat various diseases by many cultures for millennia. In mithridatism practice, individuals regularly exposed themselves to small amounts of venom until immunity developed (Valle et al., 2012). In Chinese traditional medicine, venom from the glands of *Bufo bufo gargarizans* was used for treating infection and inflammation (Meng et al., 2009; Qi et al., 2014).

Venom is a complex mixture of peptides, proteins, enzymes, salts, and non-protein constituents. In terms of numbers of species, there are currently 600 leech species (Sket and Trontelj, 2008), 800 tick species (Cabezas-Cruz and Valdes, 2014), 3,000 snake species (Wagstaff et al., 2006), 700 cone snail species (Puillandre et al., 2014), 1,100 bat species (Jan et al., 2012), 2,000 scorpion species (Cao et al., 2014), 10,000 cnidarians species (Cegolon et al., 2013) and 46,000 spider species (World_Spider_Catalog, 2017), although not all these species are venomous or dangerous to humans. Other venomous animal include centipedes, scorpions, octopus, sea anemones and fish (Fry et al., 2009). Advances in proteomic, genomic and transcriptomic platforms are rapidly defining animal venom complexity (termed venomics) and are helping facilitate the translation of venom-derived compounds to novel therapeutics (Haney et al., 2014; Safavi-Hemami et al., 2014; Undheim et al., 2013). To date, six venom-derived drugs have been approved by FDA (Table 1) and many others are in preclinical development or clinical trials (King, 2011). The majority of venoms investigated thus far have been derived from snakes, due to the large amounts of venom these species produce for research (King, 2011). However, it should be noted that the venom yield is higher in captive snakes compared to the wild snakes and the amount of venom can

be different depending on the type of bite, specifically a hunting or defensive bite (Mirtschin et al., 2006). Venoms and venom-derived compounds are known to activate or inhibit the immune response and synthetic venom-derived peptides are capable of modulating the human immune system. For example, the ShK peptide from the venom of sea anemone inhibits the Kv1.3 ion channel in T effector memory (T_{EM}) cells, producing decreased cell proliferation and suppression of IL-2 production (Beeton et al., 2005). Furthermore, a derivative of ShK (dalazatide) recently completed a successful Phase I clinical trial in psoriasis patients (Tarcha et al., 2017).

The systematic study of the venom components and their interaction with the immune system may reveal novel therapeutics for a plethora of human diseases and therapeutics against envenomation symptoms. Venoms are engaged by the immune system and a response is generated to counterbalance their effects. This recognition is chiefly mediated by inflammation combined with the release of anti-inflammatory mediators in order to maintain homeostasis (Farsky et al., 2005; Leon et al., 2011; Petricevich, 2010). Crude venom and venom-derived compounds from spider, snake, scorpion and bee venom trigger inflammation (de Lima and Brochetto-Braga, 2003; Farsky et al., 2005; Petricevich, 2010; Rahmani et al., 2014). Inflammation refers to the complex reaction to harmful or noxious stimuli, including vascular changes, cell recruitment and cytokine release. The clinical signs of inflammation include redness, pain, heat, swelling and loss of function. It is also one of the steps in healing (Voronov et al., 1999) . The immune system has evolved for approximately 1,000 million years as a defensive system to protect the host (Buchmann, 2014). Initially, innate or natural immunity protects the body with a non-specific and fast response regulated through two lines of defense. The first line is comprised of physical and chemical barriers including skin, mucosa, cilia, tears, sweat, urine and bacterial flora. When the first defense line falls the second line is activated that includes the inflammatory response. Here diverse cell types are

recruited (i.e. mast cells, neutrophils and eosinophils) and other chemical barriers such as the complement cascade are activated. The adaptive response can also be activated to generate immunological memory. Adaptive immunity is chiefly composed of T cells and B cells. T cells require antigen presentation by antigen presenting cells (APCs) via the Major Histocompatibility Complex (MHC). When APCs present antigen to T cells they become activated and secrete cytokines. B cells produce antibodies and plasma cells, the mature form of B cells, belong to the humoral immunity arm (Cota and Midwinter; Warrington et al., 2011). This review catalogues the potential of venom and their components as drugs or drug scaffolds, focusing on their potential as novel modulators of these immune cells (Figure 1).

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2. The immune response to venom

2.1 Snake venom and immune modulation

Snake venom is synthetized by glands under the eye and they comprise a cluster of proteins that are determined by diet, geography (Daltry et al., 1996), age and gender (Woltering, 2012). Snake venom proteins are mixed with other components such as enzymes, amino acids, carbohydrates, lipids, amines and metal components (i.e. Zn^+, Mg^+, K^+, Ca^+ and Na^+). Snake envenomation is a significant public health burden in tropics with over five million bites annually according to the World Health Organization (WHO) (Ahmed et al., 2008; Chippaux, 1998).

Post envenomation, venom components generate an immune response (Leon et al., 2011). Both the innate and adaptive immune arms then attempt to neutralize the venom components. The innate immune response commences first and triggers a non-specific inflammatory cascade mediated by neutrophils, eosinophils, basophils and macrophages that phagocyte antigen and release cytokines (Nicholson, 2016). Mast cells release histamine to expand the blood vessels enhancing cell recrutiment and migration. Leukocytes and mast cells produce prostaglandin D_2 (PGD_2) that vasodilates and permeabilizes vessels. Prostaglandins also stimulate nerve endings causing pain (Ricciotti and FitzGerald, 2011; Urb and Sheppard, 2012). Bradykinins are released that modify cell junctions allowing neutrophils to migrate to the site of injury (Golias et al., 2007; Sukriti et al., 2014). Nitric oxide (NO) is a gas produced by endothelial cells that functions as a signaling molecule. NO is involved in the relaxation of blood vessels and can perform mediator activities in immune cells such as macrophages, neutrophils, APCs and T cells (Coleman, 2001). Snake venom is known to induce these mediators after envenomation. For example, the venom of *Bothrops erythromelas* induces NO production in murine splenocytes (Luna et al., 2011) and the

venom from *Bothrops jararacussu* enhances neutrophil chemotaxis (Wanderley et al., 2014). Snake envenomation can cause an increase of neutrophils and lymphocyte counts and one study found that an elevated neutrophil/lymphocyte ratio correlated with longer periods of hospitalization (Elbey et al., 2017), with selective proliferation likely due snake-derivied L-amino acid oxidases (Pontes et al., 2016; Wei et al., 2009). Snake venom can induce systemic and local inflammation and it is well documented that the genus *Bothrops* can induce severe inflammation. In a murine model, the snake venom from *Bothrops asper* enhanced the production of IL-6, TNFα and eicosanoids (Zamuner et al., 2005) and venom-derived phospholipase A_2s (PLA_2s) improved phagocytic activity of macrophages *in vitro* (Rueda et al., 2013).

When the inflammatory response is generated by external dangers the complement system activates a sequence of proteins that induces cell lysis and antigen presentation to the adaptive immune system. The activation of complement is part of the innate immune response and includes more than 30 proteins (Sarma and Ward, 2011). There are three biochemical pathways; the classic pathway, the alternative pathway and lectin pathway (Sarma and Ward, 2011). The main role of the complement system is to amplify the immune response through the stimulation of phagocytosis and cell killing (Sarma and Ward, 2011). Venom from *Bothrops jararacussu* and *Bothrops pirajai* can activate the classic and lectin pathways (Ayres et al., 2015). Venom from the *Elapidae* family *Micrurus* genus can also activate a specific complement cascade that induces B cell and T cell function (Tanaka et al., 2012). A P-I metalloproteinase derived from the venom of *Bothrops pirajai* can activate complement proteins that induce mast cells to produce histamine, enhancing phagocytosis and enhancing immune cell migration (Pidde-Queiroz et al., 2013). Similarly, venom from *Daboia Russelii* can activate complement proteins and induce IL-6 and IL-10 (Stone et al., 2013). Conversely, a P-III metalloproteinase from *Naja naja atra* venom is considered an

anticomplement molecule (Sun and Bao, 2010). Another study found that *Naja naja atra* venom enhanced innate and humoral immune responses while inhibiting $CD4^+$ and $CD8^+$ T cell proliferation in response to mitogen (Kou et al., 2014). *Naja naja atra* venom also induced production of IFNγ and IL-4 and inhibited IL-17 production. Mice injected with *Crotalus durissus terrificus* venom showed increased plasma levels of IL-4, IL-5, IL-6, TNFα, IL-10 and NO (Hernandez Cruz et al., 2008) and decreased phagocytosis by neutrophils (Lima et al., 2012). A L-amino acid oxidase from *Agkistrodon blomhoffii ussurensis* venom induced IL-2, IL-6 and IL-12 from primary human monocytes and T cells (Wei et al., 2007) and a PLA_2 from *Bothrops leucurus* venom induced IL-1β, IL-6, IL-12p40 and TNFα from primary human mononuclear cells (Nunes et al., 2011). Snake venom can also suppress the immune system with *Naja kaouthia* venom able to protect against induced arthritis in rats (Gomes et al., 2010).

2.2 Scorpion venom and immune modulation

Scorpions are arthropods that have evolved for >400 million years (Ma et al., 2012) and *Buthidae* is the family with medical significance (Smith et al., 2011). Scorpion venom is comprised of proteins, enzymes, peptides, amino acids, carbohydrates, inorganic salts, lipids and amines (Quintero-Hernández et al., 2013) and shares similarities with tick and spider venom (Cordeiro et al., 2015). Scorpion venom is also rich in neurotoxins that can cause alterations in the central nervous system (Watt and Simard, 1984). Scorpion envenomation is a significant public health burden in several tropical and subtropical countries such as Brazil, (Furtado Sda et al., 2016) Mexico, (Isbister and Bawaskar 2014) and Iran (Jalali and Rahim, 2014). In addition, over one million cases are reported globally every year (Isbister and Bawaskar 2014). Clinical symptoms in envenomed patients include sweating, hypertension, nausea, extreme pain, vomiting, tachycardia and convulsions (Isbister and Bawaskar 2014) and envenomation can induce a systemic

inflammatory response syndrome, a result of abnormal cytokine production (Voronov et al., 1999) . Scorpion venom is known to interact with Na^+, K^+, Ca^+ and Cl^- ion channels (Quintero-Hernández et al., 2013).

Previous studies have shown that the main cytokines released in response to scorpion envenomation are IL-1, IL-6 and TNFα (Fukuhara et al., 2003; Jalali et al., 2011). One study showed that systemic IL-6 plays an important role in scorpion envenomation (Sofer et al., 1996). In another scorpion envenomation study, there was an increase of systemic IL-6, soluble IL-6 receptor, TNFα, and RANTES, with high levels correlating with fatal outcomes (Abdel-Haleem et al., 2006). Venom from *Androctus australis hector, Centruroides noxius* and *Tityus serrulatus* can initiate systemic IL-1 release in humans, triggering a complex cascade of other inflammatory/regulatory cytokines including IL-6, IL-10 and TNFα (Petricevich, 2010). Another study showed that *Tityus serrulatus* envenomation initiated systemic release of IL-1, IL-6, IL-8, TNFα and IL-10 (Fukuhara et al., 2003).

Cytokines can be released at different time points depending on the cytokine and the stimulus (Sullivan et al., 2000). Experiments performed on rats have shown that the plasma cytokines IL-1, IL-6 and TNFα peak three hours post injection of *Mesobuthus eupeus* venom and that antivenom can dampen the inflammatory response (Razi Jalali et al., 2015). The scorpion venom of *Tityus serrulatus* and its fractions were tested in a murine macrophage cell line pretreated with the mitogen lipopolysaccharide (LPS). Crude venom and two fractions augmented TNFα, IL-6 and NO release. In contrast, a separate fraction inhibited the release of TNFα and IL-6 and induced IL-10 suggesting anti-inflammatory activity (Zoccal et al., 2011). The venom of *Androctonus crassicauda* is known to enhance IL-12 production in human monocytes (Saadi et al., 2015). IL-12 is a pleiotropic cytokine driving T helper 1 (Th1) differentiation, IFNγ production, and T cell

proliferation (Miles et al., 2015; Saadi et al., 2015). T cells are central for anti-pathogen and anti-cancer immunity and their dysfunction underlies autoimmunity (Miles et al., 2011). Additionally, the venom of the *Hemiscorpius lepturus* induces IL-12 release from human monocytes *in vitro* (Hadaddezfuli et al., 2015) and a fraction from *Tityus serrulatus* venom induced IL-1, IL-6, TNFα and IL-10 from murine monocytes *in vitro* (Petricevich et al., 2007). Venoms can also interfere with immune cell proliferation. The venom of *Tityus serrulatus* increases IL-6 secretion in PBMC and inhibits proliferation in T cells activated by mitogen (Casella-Martins et al., 2015).

The recognition of external threat is performed by Toll-like receptors (TLRs) which are membrane-spanning proteins in the innate immune system, mainly expressed in macrophages and dendritic cells (DCs) (Kawai and Akira, 2010). TLRs are able to recognize ligands from microbes (bacteria, viruses and fungi) and then activate immune responses (Kawai and Akira, 2010). Ten TLRs have been identified in humans and TLR agonists induce activation and maturation of the immune system (Kawai and Akira, 2010).Venoms are known to engage the innate immune system including TLRs. For example, crude *Tityus serrulatus* venom and a venom fraction are sensed by murine TLR2 and TLR4 and induce the NF-κB and MAPK signaling pathways in macrophages resulting in release of IL-6, TNFα, PGE_2 and LTB_4 (Zoccal et al., 2014). *Tityus serrulatus* venom fractions have also been observed to modulate APC phenotype and function (Petricevich et al., 2008).

The interaction between venom-derived compounds and ion channels and has been well studied (King, 2011). Venom-derived peptides are highly selective for these targets, and they have been described as promising candidates for new therapeutic approaches and drug development (Bagal et al., 2013). Ion channels, specifically K^+ channels, are involved in T cell activation and are a chief target for immunomodulation. Other lineages also express K^+ channels (DCs, monocytes,

and macrophages) (Zhao et al., 2015). Scorpion venom and its components can manipulate K^+ channels for immune modulation (Hmed et al., 2013; Petricevich et al., 2007). For example, several scorpion peptides are known to inhibit K^+ ion channels (Dutertre and Lewis, 2010; Swartz, 2013) including Margatoxin (MgTX) peptide from the venom of *Centruroides margaritatus*. MgTX can inhibit Kv 1.3 channels expressed by T cells and B cells (Bartok et al., 2014; Garcia-Calvo et al., 1993). A second example is Kaliotoxin (KTx) peptide from the venom of *Androctonus mauretanicus mauretanicus* which can inhibit both Ca^+ and K^+ channels (Crest et al., 1992).

2.3 Bee Venom and immune modulation

The venom of *Apis mellifera* also has applications for immune modulation. 50-60% of the dry venom compises a single melittin peptide (Raghuraman and Chattopadhyay, 2007) and 2-3% of the dry venom comprises the apamin peptide (Gmachl and Kreil, 1995). Bee venom also contains enzymes such as hyaluronidase, PLA_2 and histamine (Hwang et al., 2015).

DCs are the chief lineage for antigen presentation and they initiate both naïve and memory T cell responses (Randolph et al., 2005). Immature DCs are able to digest antigens by endocytosis, micropinocytosis and phagocytosis and, once they uptake antigen, DC migrate to lymph nodes where they mature and encounter T cells (Randolph et al., 2005). DCs express well known surface markers and costimulatory molecules that increase in expression during maturation (CD40, CD80, CD83 and CD86) and a mature DC phenotype correlates directly with potent T cell responses (Hubo et al., 2013). PLA2 from bee venom can enhance the maturation of DC and PLA2, in combination with TNFα and IL-1β, can induce the upregulation of costimulatory molecules CD83, CD86, both important for T cell stimulation (Aerts-Toegaert et al., 2007; Jeannin et al., 2000; Van Kaer, 2015). Immune cells express classic antigen presenting molecules MHC class I and class II

but can also express non-classical molecules including CD1 (Rossjohn et al., 2015). Bee venom PLA2 can activate human T cells via CD1 molecules (Bourgeois et al., 2015) and can also induce a Th2 response via the release of IL-33 (Palm et al., 2013), a cytokine common in the skin and intestine (Miller, 2011). Thus, bee venom is a potent immune modulator and it has been used for a over a hundred years in autoimmune diseases such as rheumatoid arthritis and allergic disorders like asthma (Pak, 2016). Bee venom is known to induce T regulatory (Treg) cells (Park et al., 2015), an important regulatory lineage that corrects erroneous activities of other T cell subsets. Treg cells produce TGFβ and IL-10 that suppress the immune system and therefore reduce autoimmunity, inflammation and allergy (Wan and Flavell, 2007). Bee venom is known to induce Treg populations effectively and therapeutic application decreases inflammation of the bronchi in a murine asthma model (Choi et al., 2013).

2.4 Sea anemone toxin and immune modulation

A toxin rather than a venom, the ShK peptide from derived from the *Stoichactis helianthus* anemone (Pennington et al., 2012) shows promise as a selective immune suppressor (Norton et al., 2004). Analogs of the toxin have shown similar activities and modes of action (Lanigan et al., 2001). The anemone produces the toxin for protection against predators. Autoimmunity is the failure of the immune system to differentiate external threats from healthy operations resulting in unintended tissue damage. Most autoimmune diseases have no cures and researchers are actively exploring natural sources for novel therapeutics (Smallwood et al., 2017). The ShK peptide is known to block Kv1.3 channel found on the surface of T_{EM} cells, which are central to the damage cascade in autoimmunity (Beeton et al., 2005). The Dalazatide peptide recently underwent clinical trials in psoriasis and the patients showed an improvement of this condition. The clinical trial data has now been published (Tarcha et al., 2017).

3. Conclusions

Recent advances in omics technologies paired with advances in synthetic peptide production and rapid recombinant expression (cell-free systems) is leading to an explosion in basic and applied venomics. Indeed, an estimated 20 million venom-derived compounds are thought to remain unexplored in nature (Escoubas and King, 2009). Combining advances in venomics with progress in low cost, high-throughput screening platforms will no doubt yield hundreds of prototype compounds applicable to the ~10,000 diseases known to medicine (WHO). At present, six venom-derived drugs have been FDA approved with many more in preclinical development and in clinical trials. Current research shows that venom has the capacity to induce potent effects on the immune response. These include customizer compounds that tune immune cell numbers, phenotype and function. For instance, snake and bee venom compounds that regulate immune cell subsets numbers and cell trafficking would be useful across autoimmunity, infectious disease and cancer. Snake venom compounds that induce IL-2 and IFNγ would be useful in the emerging field of cancer immunotherapy and snake venom compounds that augment humoral immunity might be useful as adjuvants for antibody-based vaccines. Scorpion venom compounds that induce IL-12 would be useful for DC-based vaccines and snake and scorpion venom compounds that induce IL-10 might be useful in autoimmune disorders. Snake and scorpion venom compounds that selectively shut off T cell and B cell function would also be useful in autoimmune disorders and transplant medicine. Additionally, targeting these immune pathways may also open new therapeutic options that help alleviate envenomation symptoms associated with immune dysfunction. With these examples in mind, it is likely that venom-derived immune drug development is still in its infancy and these data emphasize the importance of preserving biodiversity to sustain future discoveries.

Conflict of Interest Statement

No conflicts of interest were disclosed by authors.

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References

Abdel-Haleem, A.H., Meki, A.R., Noaman, H.A., Mohamed, Z.T., 2006. Serum levels of IL-6 and its soluble receptor, TNF-alpha and chemokine RANTES in scorpion envenomed children: their relation to scorpion envenomation outcome. Toxicon : official journal of the International Society on Toxinology 47, 437-444.

Aerts-Toegaert, C., Heirman, C., Tuyaerts, S., Corthals, J., Aerts, J.L., Bonehill, A., Thielemans, K., Breckpot, K., 2007. CD83 expression on dendritic cells and T cells: correlation with effective immune responses. European journal of immunology 37, 686-695.

Ahmed, S.M., Ahmed, M., Nadeem, A., Mahajan, J., Choudhary, A., Pal, J., 2008. Emergency treatment of a snake bite: Pearls from literature. Journal of Emergencies, Trauma and Shock 1, 97-105.

Ayres, L.R., Récio, A.d.R., Burin, S.M., Pereira, J.C., Martins, A.C., Sampaio, S.V., de Castro, F.A., Pereira-Crott, L.S., 2015. Bothrops snake venoms and their isolated toxins, an L-amino acid oxidase and a serine protease, modulate human complement system pathways. The journal of venomous animals and toxins including tropical diseases 21, 29.

Bagal, S.K., Brown, A.D., Cox, P.J., Omoto, K., Owen, R.M., Pryde, D.C., Sidders, B., Skerratt, S.E., Stevens, E.B., Storer, R.I., Swain, N.A., 2013. Ion channels as therapeutic targets: a drug discovery perspective. Journal of medicinal chemistry 56, 593-624.

Bartok, A., Toth, A., Somodi, S., Szanto, T.G., Hajdu, P., Panyi, G., Varga, Z., 2014. Margatoxin is a non-selective inhibitor of human Kv1.3 K+ channels. Toxicon : official journal of the International Society on Toxinology 87, 6-16.

Beeton, C., Pennington, M.W., Wulff, H., Singh, S., Nugent, D., Crossley, G., Khaytin, I., Calabresi, P.A., Chen, C.-Y., Gutman, G.A., Chandy, K.G., 2005. Targeting Effector Memory T

Cells with a Selective Peptide Inhibitor of Kv1.3 Channels for Therapy of Autoimmune Diseases. Molecular pharmacology 67, 1369-1381.

Bourgeois, E.A., Subramaniam, S., Cheng, T.Y., De Jong, A., Layre, E., Ly, D., Salimi, M., Legaspi, A., Modlin, R.L., Salio, M., Cerundolo, V., Moody, D.B., Ogg, G., 2015. Bee venom processes human skin lipids for presentation by CD1a. J Exp Med 212, 149-163.

Buchmann, K., 2014. Evolution of Innate Immunity: Clues from Invertebrates via Fish to Mammals. Frontiers in immunology 5, 459.

Cabezas-Cruz, A., Valdes, J.J., 2014. Are ticks venomous animals? Frontiers in zoology 11, 47.

Cao, Z., Di, Z., Wu, Y., Li, W., 2014. Overview of Scorpion Species from China and Their Toxins. Toxins 6, 796-815.

Casella-Martins, A., Ayres, L.R., Burin, S.M., Morais, F.R., Pereira, J.C., Faccioli, L.H., Sampaio, S.V., Arantes, E.C., Castro, F.A., Pereira-Crott, L.S., 2015. Immunomodulatory activity of Tityus serrulatus scorpion venom on human T lymphocytes. The journal of venomous animals and toxins including tropical diseases 21, 46.

Cegolon, L., Heymann, W.C., Lange, J.H., Mastrangelo, G., 2013. Jellyfish Stings and Their Management: A Review. Marine drugs 11, 523-550.

Chippaux, J.P., 1998. Snake-bites: appraisal of the global situation. Bulletin of the World Health Organization 76, 515-524.

Choi, M.S., Park, S., Choi, T., Lee, G., Haam, K.K., Hong, M.C., Min, B.I., Bae, H., 2013. Bee venom ameliorates ovalbumin induced allergic asthma via modulating CD4+CD25+ regulatory T cells in mice. Cytokine 61, 256-265.

Coleman, J.W., 2001. Nitric oxide in immunity and inflammation. International immunopharmacology 1, 1397-1406.

Cordeiro, F.A., Amorim, F.G., Anjolette, F.A., Arantes, E.C., 2015. Arachnids of medical importance in Brazil: main active compounds present in scorpion and spider venoms and tick saliva. The journal of venomous animals and toxins including tropical diseases 21, 24.

Cota, A.M., Midwinter, M.J., The immune system. Anaesthesia & Intensive Care Medicine 16, 353-355.

Crest, M., Jacquet, G., Gola, M., Zerrouk, H., Benslimane, A., Rochat, H., Mansuelle, P., Martin-Eauclaire, M.F., 1992. Kaliotoxin, a novel peptidyl inhibitor of neuronal BK-type Ca(2+)-activated K+ channels characterized from Androctonus mauretanicus mauretanicus venom. The Journal of biological chemistry 267, 1640-1647.

Daltry, J.C., Wuster, W., Thorpe, R.S., 1996. Diet and snake venom evolution. Nature 379, 537-540.

de Lima, P.R., Brochetto-Braga, M.R., 2003. Hymenoptera venom review focusing on Apis mellifera. Journal of Venomous Animals and Toxins including Tropical Diseases 9, 149-162.

Dutertre, S., Lewis, R.J., 2010. Use of venom peptides to probe ion channel structure and function. The Journal of biological chemistry 285, 13315-13320.

Elbey, B., Baykal, B., Yazgan, Ü.C., Zengin, Y., 2017. The prognostic value of the neutrophil/lymphocyte ratio in patients with snake bites for clinical outcomes and complications. Saudi Journal of Biological Sciences 24, 362-366.

Escoubas, P., King, G.F., 2009. Venomics as a drug discovery platform. Expert Rev Proteomics 6, 221-224.

Farsky, S.H., Antunes, E., Mello, S.B., 2005. Pro and antiinflammatory properties of toxins from animal venoms. Current drug targets. Inflammation and allergy 4, 401-411.

Fry, B.G., Roelants, K., Champagne, D.E., Scheib, H., Tyndall, J.D., King, G.F., Nevalainen, T.J., Norman, J.A., Lewis, R.J., Norton, R.S., Renjifo, C., de la Vega, R.C., 2009. The toxicogenomic

multiverse: convergent recruitment of proteins into animal venoms. Annu Rev Genomics Hum Genet 10, 483-511.

Fukuhara, Y.D., Reis, M.L., Dellalibera-Joviliano, R., Cunha, F.Q., Donadi, E.A., 2003. Increased plasma levels of IL-1beta, IL-6, IL-8, IL-10 and TNF-alpha in patients moderately or severely envenomed by Tityus serrulatus scorpion sting. Toxicon 41, 49-55.

Furtado Sda, S., Belmino, J.F., Diniz, A.G., Leite Rde, S., 2016. Epidemiology of Scorpion Envenomation in the State of Ceara, Northeastern Brazil. Rev Inst Med Trop Sao Paulo 58, 15.

Garcia-Calvo, M., Leonard, R.J., Novick, J., Stevens, S.P., Schmalhofer, W., Kaczorowski, G.J., Garcia, M.L., 1993. Purification, characterization, and biosynthesis of margatoxin, a component of Centruroides margaritatus venom that selectively inhibits voltage-dependent potassium channels. The Journal of biological chemistry 268, 18866-18874.

Gmachl, M., Kreil, G., 1995. The precursors of the bee venom constituents apamin and MCD peptide are encoded by two genes in tandem which share the same 3'-exon. The Journal of biological chemistry 270, 12704-12708.

Golias, C., Charalabopoulos, A., Stagikas, D., Charalabopoulos, K., Batistatou, A., 2007. The kinin system - bradykinin: biological effects and clinical implications. Multiple role of the kinin system - bradykinin. Hippokratia 11, 124-128.

Gomes, A., Bhattacharya, S., Chakraborty, M., Bhattacharjee, P., Mishra, R., Gomes, A., 2010. Anti-arthritic activity of Indian monocellate cobra (Naja kaouthia) venom on adjuvant induced arthritis. Toxicon 55, 670-673.

Hadaddezfuli, R., Khodadadi, A., Assarehzadegan, M.A., Pipelzadeh, M.H., Saadi, S., 2015. Hemiscorpius lepturus venom induces expression and production of interluckin-12 in human monocytes. Toxicon : official journal of the International Society on Toxinology 100, 27-31.

Haney, R.A., Ayoub, N.A., Clarke, T.H., Hayashi, C.Y., Garb, J.E., 2014. Dramatic expansion of the black widow toxin arsenal uncovered by multi-tissue transcriptomics and venom proteomics. BMC Genomics 15, 366.

Hernandez Cruz, A., Garcia-Jimenez, S., Zucatelli Mendonca, R., Petricevich, V.L., 2008. Pro- and anti-inflammatory cytokines release in mice injected with Crotalus durissus terrificus venom. Mediators Inflamm 2008, 874962.

Hmed, B.N., Serria, H.T., Mounir, Z.K., 2013. Scorpion Peptides: Potential Use for New Drug Development. Journal of Toxicology 2013.

Hubo, M., Trinschek, B., Kryczanowsky, F., Tuettenberg, A., Steinbrink, K., Jonuleit, H., 2013. Costimulatory Molecules on Immunogenic Versus Tolerogenic Human Dendritic Cells. Frontiers in immunology 4.

Hwang, D.-S., Kim, S.K., Bae, H., 2015. Therapeutic Effects of Bee Venom on Immunological and Neurological Diseases. Toxins 7, 2413-2421.

Isbister , G.K., Bawaskar , H.S., 2014. Scorpion Envenomation. New England Journal of Medicine 371, 457-463.

Jalali, A., Pipelzadeh, M.H., Taraz, M., Khodadadi, A., Makvandi, M., Rowan, E.G., 2011. Serum TNF-alpha levels reflect the clinical severity of envenomation following a Hemiscorpius lepturus sting. European cytokine network 22, 5-10.

Jalali, A., Rahim, F., 2014. Epidemiological review of scorpion envenomation in iran. Iranian journal of pharmaceutical research : IJPR 13, 743-756.

Jan, C., Dawson, D.A., Altringham, J.D., Burke, T., Butlin, R.K., 2012. Development of conserved microsatellite markers of high cross-species utility in bat species (Vespertilionidae, Chiroptera, Mammalia). Mol Ecol Resour 12, 532-548.

Jeannin, P., Magistrelli, G., Aubry, J.P., Caron, G., Gauchat, J.F., Renno, T., Herbault, N., Goetsch, L., Blaecke, A., Dietrich, P.Y., Bonnefoy, J.Y., Delneste, Y., 2000. Soluble CD86 is a costimulatory molecule for human T lymphocytes. Immunity 13, 303-312.

Kawai, T., Akira, S., 2010. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nature immunology 11, 373-384.

King, G.F., 2011. Venoms as a platform for human drugs: translating toxins into therapeutics. Expert Opin Biol Ther 11, 1469-1484.

Kou, J.Q., Han, R., Xu, Y.L., Ding, X.L., Wang, S.Z., Chen, C.X., Ji, H.Z., Ding, Z.H., Qin, Z.H., 2014. Differential Effects of Naja naja atra Venom on Immune Activity. Evidence-based complementary and alternative medicine : eCAM 2014, 287631.

Lanigan, M.D., Pennington, M.W., Lefievre, Y., Rauer, H., Norton, R.S., 2001. Designed peptide analogues of the potassium channel blocker ShK toxin. Biochemistry 40, 15528-15537.

Leon, G., Sanchez, L., Hernandez, A., Villalta, M., Herrera, M., Segura, A., Estrada, R., Gutierrez, J.M., 2011. Immune response towards snake venoms. Inflammation & allergy drug targets 10, 381-398.

Lima, T.S., Cataneo, S.C., Iritus, A.C., Sampaio, S.C., Della-Casa, M.S., Cirillo, M.C., 2012. Crotoxin, a rattlesnake toxin, induces a long-lasting inhibitory effect on phagocytosis by neutrophils. Exp Biol Med (Maywood) 237, 1219-1230.

Luna, K.P.d.O., Melo, C.M., Pascoal, V.P.M., Martins Filho, O.A., Pereira, V.R.A., 2011. Bothrops erythromelas snake venom induces a proinflammatory response in mice splenocytes.

Ma, Y., He, Y., Zhao, R., Wu, Y., Li, W., Cao, Z., 2012. Extreme diversity of scorpion venom peptides and proteins revealed by transcriptomic analysis: implication for proteome evolution of scorpion venom arsenal. J Proteomics 75, 1563-1576.

Mauri, M., Kirchner, M., Aharoni, R., Ciolli Mattioli, C., van den Bruck, D., Gutkovitch, N., Modepalli, V., Selbach, M., Moran, Y., Chekulaeva, M., 2017. Conservation of miRNA-mediated silencing mechanisms across 600 million years of animal evolution. Nucleic Acids Res 45, 938-950.

Meng, Z., Yang, P., Shen, Y., Bei, W., Zhang, Y., Ge, Y., Newman, R.A., Cohen, L., Liu, L., Thornton, B., Chang, D.Z., Liao, Z., Kurzrock, R., 2009. Pilot study of huachansu in patients with hepatocellular carcinoma, nonsmall-cell lung cancer, or pancreatic cancer. Cancer 115, 5309-5318.

Miles, J.J., Douek, D.C., Price, D.A., 2011. Bias in the alphabeta T-cell repertoire: implications for disease pathogenesis and vaccination. Immunol Cell Biol 89, 375-387.

Miles, J.J., McCluskey, J., Rossjohn, J., Gras, S., 2015. Understanding the complexity and malleability of T-cell recognition. Immunol Cell Biol 93, 433-441.

Miller, A.M., 2011. Role of IL-33 in inflammation and disease. Journal of inflammation (London, England) 8, 22.

Mirtschin, P.J., Dunstan, N., Hough, B., Hamilton, E., Klein, S., Lucas, J., Millar, D., Madaras, F., Nias, T., 2006. Venom yields from Australian and some other species of snakes. Ecotoxicology (London, England) 15, 531-538.

Mora, C., Tittensor, D.P., Adl, S., Simpson, A.G.B., Worm, B., 2011. How Many Species Are There on Earth and in the Ocean? PLoS Biology 9.

Nicholson, Lindsay B., 2016. The immune system. Essays in Biochemistry 60, 275-301.

Norton, R.S., Pennington, M.W., Wulff, H., 2004. Potassium channel blockade by the sea anemone toxin ShK for the treatment of multiple sclerosis and other autoimmune diseases. Curr Med Chem 11, 3041-3052.

Nunes, D.C., Rodrigues, R.S., Lucena, M.N., Cologna, C.T., Oliveira, A.C., Hamaguchi, A., Homsi-Brandeburgo, M.I., Arantes, E.C., Teixeira, D.N., Ueira-Vieira, C., Rodrigues, V.M., 2011.

Isolation and functional characterization of proinflammatory acidic phospholipase A2 from Bothrops leucurus snake venom. Comp Biochem Physiol C Toxicol Pharmacol 154, 226-233.

Pak, S.C., 2016. An Introduction to the Toxins Special Issue on "Bee and Wasp Venoms: Biological Characteristics and Therapeutic Application". Toxins (Basel) 8.

Palm, N.W., Rosenstein, R.K., Yu, S., Schenten, D.D., Florsheim, E., Medzhitov, R., 2013. Bee venom phospholipase A2 induces a primary type 2 response that is dependent on the receptor ST2 and confers protective immunity. Immunity 39, 976-985.

Park, S., Baek, H., Jung, K.H., Lee, G., Lee, H., Kang, G.H., Lee, G., Bae, H., 2015. Bee venom phospholipase A2 suppresses allergic airway inflammation in an ovalbumin-induced asthma model through the induction of regulatory T cells. Immun Inflamm Dis 3, 386-397.

Pennington, M.W., Harunur Rashid, M., Tajhya, R.B., Beeton, C., Kuyucak, S., Norton, R.S., 2012. A C-terminally amidated analogue of ShK is a potent and selective blocker of the voltage-gated potassium channel Kv1.3. FEBS letters 586, 3996-4001.

Petricevich, V.L., 2010. Scorpion venom and the inflammatory response. Mediators of inflammation 2010, 903295.

Petricevich, V.L., Hernandez Cruz, A., Coronas, F.I., Possani, L.D., 2007. Toxin gamma from Tityus serrulatus scorpion venom plays an essential role in immunomodulation of macrophages. Toxicon : official journal of the International Society on Toxinology 50, 666-675.

Petricevich, V.L., Reynaud, E., Cruz, A.H., Possani, L.D., 2008. Macrophage activation, phagocytosis and intracellular calcium oscillations induced by scorpion toxins from Tityus serrulatus. Clinical and experimental immunology 154, 415-423.

Pidde-Queiroz, G., Magnoli, F.C., Portaro, F.C., Serrano, S.M., Lopes, A.S., Paes Leme, A.F., van den Berg, C.W., Tambourgi, D.V., 2013. P-I snake venom metalloproteinase is able to activate the

complement system by direct cleavage of central components of the cascade. PLoS Negl Trop Dis 7, e2519.

Pontes, A.S., Setubal Sda, S., Nery, N.M., da Silva, F.S., da Silva, S.D., Fernandes, C.F., Stabeli, R.G., Soares, A.M., Zuliani, J.P., 2016. p38 MAPK is involved in human neutrophil chemotaxis induced by L-amino acid oxidase from Calloselasma rhodosthoma. Toxicon 119, 106-116.

Puillandre, N., Bouchet, P., Duda, T.F., Jr., Kauferstein, S., Kohn, A.J., Olivera, B.M., Watkins, M., Meyer, C., 2014. Molecular phylogeny and evolution of the cone snails (Gastropoda, Conoidea). Mol Phylogenet Evol 78, 290-303.

Qi, J., Tan, C.K., Hashimi, S.M., Zulfiker, A.H., Good, D., 2014. Toad glandular secretions and skin extractions as anti-inflammatory and anticancer agents. 2014, 312684.

Quintero-Hernández, V., Jiménez-Vargas, J.M., Gurrola, G.B., Valdivia, H.H.F., Possani, L.D., 2013. Scorpion venom components that affect ion-channels function. Toxicon : official journal of the International Society on Toxinology 76, 328-342.

Raghuraman, H., Chattopadhyay, A., 2007. Melittin: a membrane-active peptide with diverse functions. Bioscience reports 27, 189-223.

Rahmani, F., Banan Khojasteh, S.M., Ebrahimi Bakhtavar, H., Rahmani, F., Shahsavari Nia, K., Faridaalaee, G., 2014. Poisonous Spiders: Bites, Symptoms, and Treatment; an Educational Review. Emergency 2, 54-58.

Randolph, G.J., Angeli, V., Swartz, M.A., 2005. Dendritic-cell trafficking to lymph nodes through lymphatic vessels. Nature reviews. Immunology 5, 617-628.

Razi Jalali, M., Jalali, M.T., Mapar, Z., 2015. Evaluation of Plasma Cytokine Levels in Mesobuthus Eupeus (Scorpionida: Buthidae) Scorpion Envenomation in Rats Treated With Polyvalent Antivenom. Jundishapur J Health Sci 7, e27159.

Ricciotti, E., FitzGerald, G.A., 2011. Prostaglandins and Inflammation. Arteriosclerosis, thrombosis, and vascular biology 31, 986-1000.

Rossjohn, J., Gras, S., Miles, J.J., Turner, S.J., Godfrey, D.I., McCluskey, J., 2015. T cell antigen receptor recognition of antigen-presenting molecules. Annual review of immunology 33, 169-200.

Rueda, A.Q., Rodriguez, I.G., Arantes, E.C., Setubal, S.S., Calderon Lde, A., Zuliani, J.P., Stabeli, R.G., Soares, A.M., 2013. Biochemical characterization, action on macrophages, and superoxide anion production of four basic phospholipases A2 from Panamanian Bothrops asper snake venom. Biomed Res Int 2013, 789689.

Saadi, S., Assarehzadegan, M.A., Pipelzadeh, M.H., Hadaddezfuli, R., 2015. Induction of IL-12 from human monocytes after stimulation with Androctonus crassicauda scorpion venom. Toxicon : official journal of the International Society on Toxinology 106, 117-121.

Safavi-Hemami, H., Hu, H., Gorasia, D.G., Bandyopadhyay, P.K., Veith, P.D., Young, N.D., Reynolds, E.C., Yandell, M., Olivera, B.M., Purcell, A.W., 2014. Combined proteomic and transcriptomic interrogation of the venom gland of Conus geographus uncovers novel components and functional compartmentalization. Mol Cell Proteomics 13, 938-953.

Sarma, J.V., Ward, P.A., 2011. The Complement System. Cell and tissue research 343, 227-235.

Sket, B., Trontelj, P., 2008. Global diversity of leeches (Hirudinea) in freshwater. Hydrobiologia 595, 129-137.

Smallwood, T.B., Giacomin, P.R., Loukas, A., Mulvenna, J.P., Clark, R.J., Miles, J.J., 2017. Helminth Immunomodulation in Autoimmune Disease. Front Immunol 8, 453.

Smith, J.J., Hill, J.M., Little, M.J., Nicholson, G.M., King, G.F., Alewood, P.F., 2011. Unique scorpion toxin with a putative ancestral fold provides insight into evolution of the inhibitor cystine knot motif. Proceedings of the National Academy of Sciences of the United States of America 108, 10478-10483.

Sofer, S., Gueron, M., White, R.M., Lifshitz, M., Apte, R.N., 1996. Interleukin-6 release following scorpion sting in children. Toxicon : official journal of the International Society on Toxinology 34, 389-392.

Stone, S.F., Isbister, G.K., Shahmy, S., Mohamed, F., Abeysinghe, C., Karunathilake, H., Ariaratnam, A., Jacoby-Alner, T.E., Cotterell, C.L., Brown, S.G.A., 2013. Immune Response to Snake Envenoming and Treatment with Antivenom; Complement Activation, Cytokine Production and Mast Cell Degranulation. PLoS Negl Trop Dis 7, e2326.

Sukriti, S., Tauseef, M., Yazbeck, P., Mehta, D., 2014. Mechanisms regulating endothelial permeability. Pulmonary Circulation 4, 535-551.

Sullivan, K.E., Cutilli, J., Piliero, L.M., Ghavimi-Alagha, D., Starr, S.E., Campbell, D.E., Douglas, S.D., 2000. Measurement of Cytokine Secretion, Intracellular Protein Expression, and mRNA in Resting and Stimulated Peripheral Blood Mononuclear Cells. Clinical and Diagnostic Laboratory Immunology 7, 920-924.

Sun, Q.Y., Bao, J., 2010. Purification, cloning and characterization of a metalloproteinase from Naja atra venom. Toxicon 56, 1459-1469.

Swartz, K.J., 2013. The scorpion toxin and the potassium channel. eLife 2, e00873.

Tanaka, G.D., Pidde-Queiroz, G., Furtado, M.d.F.D., van den Berg, C., Tambourgi, D.V., 2012. Micrurus snake venoms activate human complement system and generate anaphylatoxins. BMC Immunology 13, 4.

Tarcha, E.J., Olsen, C.M., Probst, P., Peckham, D., Munoz-Elias, E.J., Kruger, J.G., Iadonato, S.P., 2017. Safety and pharmacodynamics of dalazatide, a Kv1.3 channel inhibitor, in the treatment of plaque psoriasis: A randomized phase 1b trial. PLoS One 12, e0180762.

Undheim, E.A., Sunagar, K., Herzig, V., Kely, L., Low, D.H., Jackson, T.N., Jones, A., Kurniawan, N., King, G.F., Ali, S.A., Antunes, A., Ruder, T., Fry, B.G., 2013. A proteomics and

transcriptomics investigation of the venom from the barychelid spider Trittame loki (brush-foot trapdoor). Toxins (Basel) 5, 2488-2503.

Urb, M., Sheppard, D.C., 2012. The Role of Mast Cells in the Defence against Pathogens. PLoS Pathogens 8, e1002619.

Valle, G., Carmignani, M., Stanislao, M., Facciorusso, A., Volpe, A.R., 2012. Mithridates VI Eupator of Pontus and mithridatism. Allergy 67, 138-139; author reply 139-140.

Van Kaer, L., 2015. Bee venom stirs up buzz in antigen presentation. The Journal of Experimental Medicine 212, 126-126.

Voronov, E., Apte, R.N., Sofer, S., 1999. The systemic inflammatory response syndrome related to the release of cytokines following severe envenomation. Journal of Venomous Animals and Toxins including Tropical Diseases, 5-33.

Wagstaff, S.C., Laing, G.D., Theakston, R.D., Papaspyridis, C., Harrison, R.A., 2006. Bioinformatics and multiepitope DNA immunization to design rational snake antivenom. PLoS Med 3, e184.

Wan, Y.Y., Flavell, R.A., 2007. 'Yin-Yang' functions of TGF-β and Tregs in immune regulation. Immunological reviews 220, 199-213.

Wanderley, C.W., Silva, C.M., Wong, D.V., Ximenes, R.M., Morelo, D.F., Cosker, F., Aragao, K.S., Fernandes, C., Palheta-Junior, R.C., Havt, A., Brito, G.A., Cunha, F.Q., Ribeiro, R.A., Lima-Junior, R.C., 2014. Bothrops jararacussu snake venom-induces a local inflammatory response in a prostanoid- and neutrophil-dependent manner. Toxicon 90, 134-147.

Warrington, R., Watson, W., Kim, H.L., Antonetti, F.R., 2011. An introduction to immunology and immunopathology. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology 7 Suppl 1, S1.

Watt, D.D., Simard, J.M., 1984. Neurotoxic Proteins in Scorpion Venom. Journal of Toxicology: Toxin Reviews 3, 181-221.

Wei, X.L., Wei, J.F., Li, T., Qiao, L.Y., Liu, Y.L., Huang, T., He, S.H., 2007. Purification, characterization and potent lung lesion activity of an L-amino acid oxidase from Agkistrodon blomhoffii ussurensis snake venom. Toxicon 50, 1126-1139.

Wei, J.F., Yang, H.W., Wei, X.L., Qiao, L.Y., Wang, W.Y., He, S.H., 2009. Purification, characterization and biological activities of the L-amino acid oxidase from Bungarus fasciatus snake venom. Toxicon 54, 262-271.

Woltering, J.M., 2012. From Lizard to Snake; Behind the Evolution of an Extreme Body Plan. Current Genomics 13, 289-299.

World_Spider_Catalog, 2017. World Spider Catalog. http://wsc.nmbe.ch, version 18.5.

Zamuner, S.R., Zuliani, J.P., Fernandes, C.M., Gutierrez, J.M., de Fatima Pereira Teixeira, C., 2005. Inflammation induced by Bothrops asper venom: release of proinflammatory cytokines and eicosanoids, and role of adhesion molecules in leukocyte infiltration. Toxicon : official journal of the International Society on Toxinology 46, 806-813.

Zhao, Y., Huang, J., Yuan, X., Peng, B., Liu, W., Han, S., He, X., 2015. Toxins Targeting the K(V)1.3 Channel: Potential Immunomodulators for Autoimmune Diseases. Toxins (Basel) 7, 1749-1764.

Zoccal, K.F., Bitencourt Cda, S., Paula-Silva, F.W., Sorgi, C.A., de Castro Figueiredo Bordon, K., Arantes, E.C., Faccioli, L.H., 2014. TLR2, TLR4 and CD14 recognize venom-associated molecular patterns from Tityus serrulatus to induce macrophage-derived inflammatory mediators. PloS one 9, e88174.

Zoccal, K.F., Bitencourt Cda, S., Secatto, A., Sorgi, C.A., Bordon Kde, C., Sampaio, S.V., Arantes, E.C., Faccioli, L.H., 2011. Tityus serrulatus venom and toxins Ts1, Ts2 and Ts6 induce macrophage

activation and production of immune mediators. Toxicon : official journal of the International Society on Toxinology 57, 1101-1108.

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Table 1. FDA approved therapeutics from venom-derived proteins

*Bydureon is the long-action mode and derived of Byetta®. The administration of these drugs is in combination with other Diabetes Type 2 medications. Adapted from (King, 2011).

Name	Active Ingredients	Indication and Mechanism of Action	Route	Year	Derived from
Prialt®	Ziconotide SNX-111 Non-opioid and analgesic medication	**Severe and Chronic Pain with Neuropathic Origin** The obstruction of the ion channel by the chemical composition of the drug impedes the secretion of neurotransmisors, blocking the signal of pain to the brain.	Intrathecal administration	2004	Cone snail *Conus magus*
Byetta®	Exenatide Synthetic	**Diabetes Type 2** Increases the release of glucose-dependent insulin by the stimulation of pancreatic beta-cells. Delays gastric emptying.	Subcutaneous administration	2005	Gila Monster *Heloderma suspectum*
*Bydureon®	Exenatide Synthetic		Subcutaneous administration	2012	Gila Monster *Heloderma suspectum*
Angiomax®	Bivalirudin	**Anticoagulant** Inhibits clot formation, interacts with thrombin in cascade coagulation.	Intravenous administration	2000	Medicinal Leech *Hirudo medicinalis*
Capoten®	Captopril	**Hypertension** Interfering in the transformation between angiotensin I and Angiotensin II by the inhibition of angiotensin converting enzyme (ACE).	Oral, tablet	1981	Viper Snake *Bothrops jararaca*
Aggrastat®	Tirofiban Hidrochloride	**Inhibitor of platelet aggregation** This drug binds to the main platelet surface receptor (GP IIb/IIIa).	Intravenous administration	1999	Viper Snake *African saw-scaled*
Integrilin®	Eptifibatide	**Antiplatelet Drug** Reduces the binding of fibrinogen von Willebrand factor and ligands to GP IIb/IIIa.	Intravenous administration	1998	Viper Snake *Sistrurus miliarius barbouri*

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Figure 1. Immune pathways modulated by venom

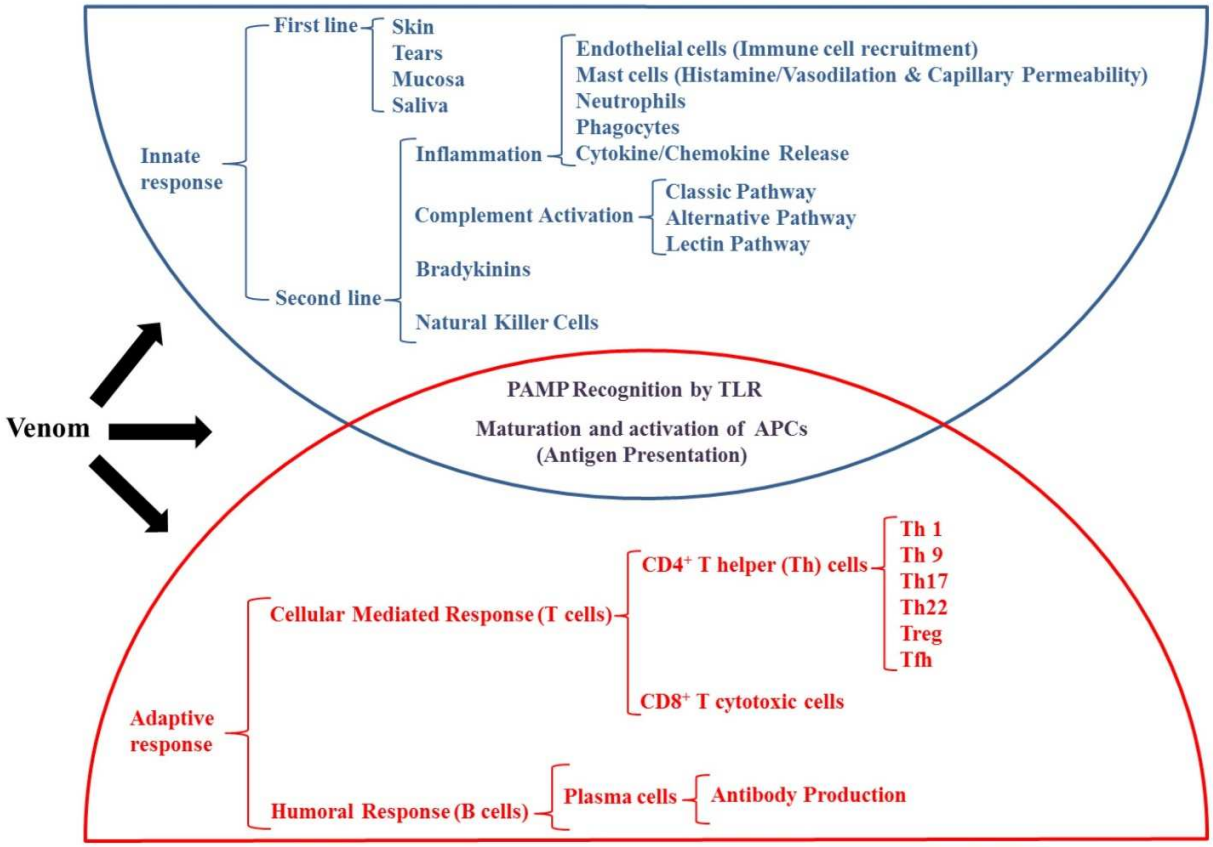

Figure 1. Immune pathways modulated by venom. The innate (blue) and adaptive (red) immune arms can be modulated by crude venom and venom components. Cells at the junction of the innate and adaptive immune arms, including DCs and APCs (black), can also be modulated by venom and venom components. The ability to selectively target each of these subsystems using synthetically-derived venom components will open novel immunotherapies across infectious disease, cancer and autoimmunity.

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