Venom peptides – A comprehensive translational perspective in pain management

Vidya V a, Raghu Ram Achar b,3, Himathi M.U. b, Akshita N b, Yogish Somayaji T c, Vivek Hamse Kameshwar d,e,*,1, K. Byrappa e,g,2,*, Dinesha Ramadas f

a K. S Hegde Medical Academy, NITTE (Deemed to be) University, Mangalore 575015, Karnataka, India
b Division of Biochemistry, School of Life Sciences, JSS Academy of Higher Education & Research, S.S. Nagar, Mysuru 570 015, Karnataka, India
c Department of Post Graduate Studies and Research in Biochemistry, St. Aloysius College (Autonomous), Mangalore 575003, Karnataka, India
d School of Natural Science, Adichunchanagiri University, B.G. Nagar-571448, Nagamangala, Mandya, India
e School of Natural Sciences, ACU-CRI, Adichunchanagiri University, BGSIT Campus, B.G. Nagar-571448, Nagamangala, Mandya, India
f School of Natural Sciences, Adichunchanagiri University, B.G. Nagar-571448, Nangamangala, Mandya, India
g Center for Material Science and Technology, Vijnana Bhavan, University of Mysore, Mysuru, Karnataka, India

Keywords: Pain, Peptides, Inflammation, Toxins, Toxicity, Management, Diabetes, Cardiovascular diseases, Antimicrobial activity

ABSTRACT

Venom peptides have been evolving complex therapeutic interventions that potently and selectively modulate a range of targets such as ion channels, receptors, and signaling pathways of physiological processes making it potential therapeutic. Several venom peptides were deduced in vivo for clinical development targeting pain management, diabetes, cardiovascular diseases, antimicrobial activity. Several contributions have been detailed for a clear perspective for a better understanding of venomous animals, their venom, and their pharmacological effects. Here we unravel and summarize the recent advances in wide venom peptides across varieties of species for their therapeutics prospects.

Contents

Introduction .................................................................................................................................................. 330
Methodology .............................................................................................................................................. 331
Bee venom-Mellitin .................................................................................................................................. 331
Cobra venom-Captopril ......................................................................................................................... 331
Scorpion venom-Chlorotoxin ................................................................................................................ 331
Centipede venom-Histamine .................................................................................................................. 334
Marine cone snail-Conotoxin ................................................................................................................ 334
Lizard venom-Exenatide ......................................................................................................................... 334
Leech venom-Bivalirudin ....................................................................................................................... 334
Saw-scaled viper snake-Tirofiban ......................................................................................................... 334
Honey bee venom-Apitoxin .................................................................................................................. 334
Cobra venom-Cobrotoxin ...................................................................................................................... 334
Leech venom-Desirudin ......................................................................................................................... 334
Jararaca pit viper snake venom-Enalapril .............................................................................................. 335
Pygmy rattle snake venom-Eptifibatide ............................................................................................... 335
Gila monster lizard venom-Lixisenatide .............................................................................................. 335
Conc snail venom-Ziconotide .............................................................................................................. 335

* Corresponding authors at: School of Natural Sciences, ACU-CRI, Adichunchanagiri University, BGSIT Campus, B.G. Nagar-571448, Nagamangala, Mandya, India (V.H. Kameshwar); Adichunchanagiri University, BGSIT Campus, B.G. Nagar-571448, Nagamangala, Mandya, India (Byrappa, K).
E-mail addresses: vivekhamse@acu.ac.in (V.H. Kameshwar), kbyrappa@gmail.com (K. Byrappa).
1 ORCID: 0000-0001-6194-9496.
2 ORCID: 0000-0002-5808-5583.
3 ORCID: 0000-0001-8196-3703.

https://doi.org/10.1016/j.crtox.2021.09.001
Received 2 August 2021; Revised 2 September 2021; Accepted 8 September 2021
Available online xxxx

2666-027X/© 2021 The Author(s). Published by Elsevier B.V.
This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
V. V et al. Current Research in Toxicology 2 (2021) 329-340

Introduction

Several toxins have evolved among plants, animals, and microbes, as a part of their defence and to capture their prey (Lewis and Garcia, 2003). Many of these toxins are identified as peptides by nature. As many of such peptides are being established as highly selective and are relatively safer potent therapeutics (Pennington et al., 2018). The non-peptide toxins are typically orally active whereas the peptide toxins are found usually in animal venoms that are associated with special organs that are meant to deliver them via intramuscular, subcutaneous, or intravenous routes (Lewis and Garcia, 2003).

The venom of spiders, wasps, scorpions, and snakes is comprised of deadly substances that are released as peptides by nature. As a part of their defence, they are used as weapons to capture their prey (Lewis and Garcia, 2003). These toxins have the potential to be used as drugs (Pennington et al., 2018). As the overall number of these venom-derived bioactive peptides that are progressing successfully towards the treatment is still limited in the current therapeutic field, their prospects tend to be very promising (Pennington et al., 2018).

Snake venoms are advance killer machines, which are pharmacologically characterized natural toxins. They act on a myriad of exogenous targets such as ion channels, receptors and enzymes within cells or on the cell membrane. Daboia russelli (Russell’s viper) (Kameshwar et al., 2017); Bungarus caeruleus (Law et al., 2014); Echis carinatus (Katkar et al., 2014), and Naja naja (Neema et al., 2020) are the most perilous snakes in Indian subcontinent causing morbidity and mortality and also one among the big four family of venomous snake. The pathophysiology of Daboia russelli envenomation includes intense local effects (hemorrhage, edema, myonecrosis and alterations in coagulant system) and systemic effects (myotoxicity, neurotoxicity and systemic bleeding) (Nijaguna Prasad et al., 1996).

The toxins from the venoms can be either cytotoxins, cardiotoxin, hemotoxins, myotoxins, nephrotoxins, and neurotoxins. Snake venom sPLA₂ from Elapidae and Hydrophididae family belongs to the group I of sPLA₂, whereas Viperidae and Crotalidae to group II, which is further subdivided into two main subgroups, depending on the residue at position 49 in the primary structure: D49 which are enzymatically active and K49 which possess low or no enzymatic activity (Lomonte and Calderón, 2003). Isoforms of sPLA₂ which are predominately involved in inflammatory cascades of variety of tissue and cells are highly up regulated in response to inflammatory stimuli. Southern Indian regional Daboia russelli venom contains sPLA₂ which are highly toxic and it constitute about 70% in the whole venom protein when compared to northern, western and eastern regions (Jayanti et al., 1989).

Phospholipase A₂ (PLA₂) enzyme cleaves fatty acids at the sn-2 position of glycerol backbone phospholipids releasing free fatty acid and lysophospholipid (Kameshwar et al., 2017; Dennis, 2000; Vivek et al., 2014). Isoforms of sPLA₂ predominately involved in inflammatory cascade in variety of tissue and cells are highly up regulated in response to inflammatory stimuli both by external and internal is categorized as group as GIIa sPLA₂ (Group-IIa sPLA₂) enzyme. The reaction is of particular importance when the fatty acid released from the sn-2 position is arachidonic acid. Arachidonic acid can be oxida-tively metabolized by cyclooxygenase and lipoxygenase enzymes to prostaglandins, thromboxanes, prostacyclins and leukotrienes, which are the mediators of inflammation. Lysophospholipid containing a choline head group and an alkyl linkage in sn-1 position act as the proinflammatory mediator for platelet activating factor, these proinflammatory molecules enhances the severity of inflammation (Dennis, 2000; Burke and Dennis, 2009; Dileep and Sadasivan, 2011).

Pain is one of the common features experienced in most injuries and tissue damage. At present, the International Association for the Study of Pain (IASP) has defined pain as “An unpleasant sensory and emotional experience that is associated with actual or potential tissue damage or described in terms of such damage” (Raja et al., 2020). The venomous organisms have been frequently stereotyped as pain-inflicting and causing distresses which have been historically vilified by mankind. Surprisingly the same venoms that can cause pain if directly injected into a host animal can turn into next-generation analgesia when injected by a clinician (Trim and Trim, 2013). Pain is said to be the most common feature of any disease, that may accompany us to be the most common feature of any disease, that may accompany us from an early age with its protective mechanism while the body responds to any harmful stimulus (Swieboda et al., 2013). Pain is not only a direct output of nociception but also interacts with several
inputs such as attention, affective dimensions, autonomic variables, immune variables, and more (Cortelli et al., 2013).

Based on their characteristic features, pain can be classified into acute pain, chronic pain, somatic pain, visceral pain, neuropathic pain, allodynia, hyperalgesia, and referred pain. Among these, chronic pain has been notoriously defined as the pain which can last much longer than its usual course of acute injury in any disease condition or the pain that may recur for months or years (Raffaeli and Arnaudo, 2017).

The general physiological process involved in mediating the pain is as follows (Cortelli et al., 2013):

- During any injury, an “inflammatory soup” is generally produced at the site of injury to stimulate and activate the nociceptors

- The afferent nociceptors from the periphery can transmit noxious signals to the projection neurons that are located in the dorsal horn of the spinal cord

- Cells in the dorsal horn are present as layers of physiologically distinct sections which are referred to as laminae. A subset of these projection neurons which are based on the type of synapse in the laminae formed by the nociceptive fibre can relay the information to the somatosensory cortex through the thalamus that can provide information about the spatial features and the intensity of the painful stimulus

- These projection neurons can engage the cingulate and insular cortices via connections with the parabrachial nucleus of the brainstem along with the amygdala is considered to be the ascending pathway that initiates the conscious perception of pain

- The ascending information can also prompt the neurons of the rostral ventral medulla and midbrain periaqueductal gray which can engage the descending feedback systems to regulate the output from the spinal cord

- Modulate pain sensation

The modulatory event may take place at all the levels of nociceptive pathways via the primary afferent neuron, dorsal horn, and higher brain centers through up-regulation or down-regulation (Yam et al., 2018). The release of hormones and other substances such as endogenous opioids, GABA, glycine may have analgesic properties to limit pain sensation whereas, chemicals such as substance P (SP), glutamate, and aspartate can act on the spinal cord and excite the perception of pain (Cortelli et al., 2013).

The opioid receptors are localized in the peripheral and central nervous systems primarily within the pain pathways (Thobois et al., 2018). The most common μ receptors are present in the thalamus, striatum, locus coeruleus, while δ receptors can be located in the cortex, striatum, pons, and the κ ones may be found in the hypothalamus, nucleus accumbens, substantia nigra, ventral tegmental area, and solitary tract nucleus (Thobois et al., 2018). Most of the pharmacologically useful proteins that can be represented as target classes for pain therapeutics are generally G-protein-coupled receptors (GPCRs), or enzymes, or ion channels and can be even growth factors (Trim and Trim, 2013). The GPCRs are commonly used as drug targets along with ion channel and enzyme inhibitors such as cyclooxygenases (COX). A number of these venom peptide analogues are being studied and have been shown to possess a potential role that can target specific classes of the pain mediating pathway.

Methodology

This systematic review aimed to study the various venom in pain management. Several research articles are being published related to venom in pain management/ antinociception therapeutics in electronic form in international database of Scopus, Pubmed, Google Scholar and Science Direct from 2000 until 2021 were investigated. Search using Nociception, pain, venom, toxins, ion channel, analgesic, venomics, peptides, proteins, and FDA keywords with and/or operators in title and abstract was conducted. Studies results are reported in table with discussion.

Bee venom-Melittin

Many studies have shown that melittin has potential glucose and lipid-lowering properties which mediates via several mechanistic pathways. The major anti-diabetes property of melittin is by increasing insulin secretion by depolarizing the pancreatic β-cells (Hossen et al., 2017). In another study by Duffy et al., reported that honey bee venom and melittin were found to suppress the activation of EGFR and HER2 by causing interference with their receptor phosphorylation in the plasma membrane studied in breast cancer cells. Further mutational studies found that the positive charge on the C-terminal sequence of melittin mediated the interaction with plasma membrane interaction and the anticaner property (Duffy et al., 2020) (Table 1). Melittin was able to reduce cell viability in leukemia cell lines such as acute lymphoblastic leukemia (CCRF-CEM) and chronic myelogenous leukemia (K-562) by inducing apoptosis via the intrinsic/mitochondrial pathway (Ceremuga et al., 2020). Melittin was also shown to be fast-acting on cancer cell lines; was found to mediate cell membrane changes within one minute of exposure in AGS, COLO205, and HCT-15 cell lines (Soliman et al., 2019). In vitro studies have also shown melittin to exhibit antibacterial activity that was more pronounced against MRSA strains, in comparison with other Gram positive bacteria; further in vivo studies also showed MRSA infected mice treated with melittin, successfully exhibited recovery from MRSA infected skin wounds (Choi et al., 2015).

Cobra venom-Captopril

In the early 1980’s the discovery of the ACE inhibitors and the isolation of captopril was one of the huge advancements in cardiovascular medicine, alongside the then used beta-blockers, calcium channel blockers, and statins (Péterfi et al., 2019). Captopril was the first ACE inhibitor approved for human use in 1981 which was developed based on the structure of bradykinin potentiating peptide that was isolated from the venom of the Brazilian pit viper, Bothrops jararaca (Péterfi et al., 2019). Captopril was designed as a miniature version of the original molecule due to its cost of isolation and inability to administer orally; with the addition of a succinyl group to a proline residue, thereby allowing its oral administration (Bordon, 2020). This amino acid residue which was found at the C-terminal of BPP5a is one of the most active peptides of bradykinin potentiating factor which was found to be responsible for interacting with ACE (Bordon, 2020) (Table 1). Captopril was added to standard therapy after acute myocardial infarction found that early or late administration improved survival and reduced cardiovascular morbidity, especially in selected high-risk patients (Plosker and McTavish, 1995).

Scorpion venom-Chlorotoxin

Scorpion venom Chlorotoxin isolated from the Israeli scorpion Leiurus quinquestriatus; belongs to a family of chlorotoxin (CTX)-like peptides (Table 1) has been known for insecticidal activity, has potential ability to interact specifically with brain cell tumors such
| Sl no | Name of the molecule | Source | Sequence | Molecular Weight | Target | Status of the research | Drug approved/designed | Marketing | Reference |
|-------|----------------------|--------|----------|------------------|--------|-----------------------|------------------------|-----------|-----------|
| 1     | Melittin             | *Apis mellifera* | GIGAVLKVLVPALSWIKRRRQQ | 2846.5 Da | Lymphatic System | Experimental Evidence At Protein Level | Approved | Prescription | [https://pubchem.ncbi.nlm.nih.gov/compound/Melittin](https://pubchem.ncbi.nlm.nih.gov/compound/Melittin) |
| 2     | Captopril            | *Bothrops jararaca* | APGGIPPPAMA | 217.29 Da | Angiotensin-Converting Enzyme, 72 Kda Type Iv Collagenase | Completed | Approved | Prescription | [https://pubchem.ncbi.nlm.nih.gov/compound/44093](https://pubchem.ncbi.nlm.nih.gov/compound/44093) |
| 3     | Chlorotoxin          | *Latarus quinquestriatus* | MCMPCTFDH QMARKCDDCC GGKGRGKICYG PQCLCR | 3996 Da | Glioblastoma | Experimental Evidence At Protein Level | Not approved | Research use only | [https://www.uniprot.org/uniprot/P60770](https://www.uniprot.org/uniprot/P60770) |
| 4     | SLPTX Family         | *Ethmostigmus rubripes* | MAPQQYLLSFALVVLYAVFD PCPSDCXCVRSNQCRPV NDEVPHNPVCNHYCIGVHLAER EQRPELPGHA WDDSEEEKDS EASLA | 111.148 Da | Histamine H1 Receptor, Histamine H2 Receptor | Experimental Evidence At Protein Level | Not approved | Research use only | [https://www.uniprot.org/uniprot/A0A023VZH1](https://www.uniprot.org/uniprot/A0A023VZH1) |
| 5     | Conotoxin M I        | *Conus magus* | GRCHHACGKNYS | 1437.6 Da | Voltage-Gated Sodium Channels | Experimental Evidence At Transcript Level | Investigational Research use only | Nordic National Prescription | [https://www.uniprot.org/uniprot/PO1521](https://www.uniprot.org/uniprot/PO1521) |
| 6     | Exenatide            | *Lacertilia* | HEGITFSDLSKQMEEEAVRLFIELWKNGGPSSGAPPSS | 4187 Da | Glucagon-Like Peptide 1 Receptor | Experimental Evidence At Protein Level | Approved | Prescription | [https://pubchem.ncbi.nlm.nih.gov/compound/45588096](https://pubchem.ncbi.nlm.nih.gov/compound/45588096) |
| 7     | Bivalirudin           | *Hirudinea* | FPRPGGGGGNDGFPREEEYL | 2180.317 Da | Prothrombin | No Information Is Available On The Use Of Bivalirudin, An Alternative Drug Is Preferred | Approved | Prescription | [https://pubchem.ncbi.nlm.nih.gov/compound/36109704](https://pubchem.ncbi.nlm.nih.gov/compound/36109704) |
| 8     | Tirofiban            | *Zulu* | AGA | 440.60 Da | Integrin Alpha-Iib, And Integrin Beta-3 | Completed | Approved | Prescription | [https://pubchem.ncbi.nlm.nih.gov/compound/60947](https://pubchem.ncbi.nlm.nih.gov/compound/60947) |
| 9     | Apitoxin             | *Apis mellifera* | GLGVLLVTGLPALSEILALAGG | 2803.4 Da | Central Nervous System | Completed | Approved | Prescription | [https://pubchem.ncbi.nlm.nih.gov/compound/16129703](https://pubchem.ncbi.nlm.nih.gov/compound/16129703) |
| 10    | Cobrotoxin           | *Naja Naja* | LECHNQQSQQTPTTTGCRCETCYKKBWRD HGYRTERGCGPSCVNYGEICCCCTDDRCNN | 6957 Da | Acetylcholine Receptor Inhibiting Toxin, Ion Channel Impairing Toxin, Neurtoxin, Postsynaptic Neurotoxin. | Experimental Evidence At Protein Level | Approved | Prescription | [https://www.uniprot.org/uniprot/133082063](https://www.uniprot.org/uniprot/133082063) |
| 11    | Desirudin            | *Hirudinea* | VVYTDCTESGNLICCEGSSCIGNQCNICLQSIDGE KNQCVTGETPKQPQHNDGDGEEPEELYQ | 6963.52 Da | No Target Organ | Completed | Approved in some cases | It is used only for research and educational purposes. | [https://pubchem.ncbi.nlm.nih.gov/compound/16129703](https://pubchem.ncbi.nlm.nih.gov/compound/16129703) |
| 12    | Enalapril            | *Bothrops jararaca* | Unik-A-P-OH | 376.453 Da | Angiotensin Converting-Enzymes | Completed | Approved | Prescription | [https://pubchem.ncbi.nlm.nih.gov/compound/5388962](https://pubchem.ncbi.nlm.nih.gov/compound/5388962) |
| 13    | Epitifibatide         | *Sistrurus miliarius* | CXGDWPSC | 832.0 Da | Integrin Beta-3 | Ongoing | Approved | Prescription | [https://pubchem.ncbi.nlm.nih.gov/compound/448812](https://pubchem.ncbi.nlm.nih.gov/compound/448812) |
| 14    | Lixisenatide         | *Heloderma suspectum* | HEGITFSDLSKQMEEEAVRLFIELWKNGGPSGAPPSSSKKKE | 4658.56 Da | Glucagon Like Peptide-1 Receptor | Completed | Approved | Prescription | [https://pubchem.ncbi.nlm.nih.gov/compound/90472060](https://pubchem.ncbi.nlm.nih.gov/compound/90472060) |
| Sl no | Name of the molecule | Source | Sequence | Molecular Weight | Target | Status of the research | Drug approved/designed | Marketing | Reference |
|-------|----------------------|--------|----------|------------------|--------|------------------------|------------------------|-----------|-----------|
| 15    | Ziconotide            | Conus magus | CKGKGA|CKSRLMYDCTCTGSCRSGLC (synthetic) | 2639.2 Da | Voltage-Dependent N-Type Calcium Subunit Alpha-1B, And Voltage-Dependent P/Q-Type Calcium Channel Subunit Alpha-1A | Withdrawn / Recruiting | Approved | Prescription | https://pubchem.ncbi.nlm.nih.gov/compound/16135415 |
| 16    | Vespid chemotactic peptide T | Vespa tropica | FLPLGKGLGGL | 1,354 Da | Inflammatory Cells | Ongoing | Approved | Prescription | https://www.uniprot.org/uniprot/P17231 |
| 17    | Mastoparan            | Wasp venom | INIKALAALAKKIL | 1,478.9 Da | Increases Gpase Activity And Purifies Gp Binds Protein | Experimental Evidence At Protein Level | Investigation is in process | Research Use only | https://pubchem.ncbi.nlm.nih.gov/compound/6324633 |
| 18    | Protonectin           | Protonectrina sylveirae | ILGITGILGLK | 28,189 Da | Defence Response To Bacterium | Experimental Evidence At Protein Level | Approved | Prescription | https://www.uniprot.org/uniprot/D2Y2D7 |
| 19    | Hainantoxin           | Haploplema hainanum | MKASMLALT GLALPVGCVY ASESEKEEKS NELSSSLAV DDNSREGRCE CLECGKCGNP SNDQCQCKSEI | 9,535 Da | Ion Channel Impairing Toxin, Neurotoxin, Pre-Synaptic Neurotoxin, Voltage-Gated Sodium Channel Impairing Toxin | Defibrinogenating Agent | Not Yet Recruiting | Not approved | Not available | https://www.uniprot.org/uniprot/P0C1R1 |
| 20    | Batrosobin            | Bodrops atrox mojensi | VIGGDECIDIN EPPLAFLNY SPFLFGMPLTL INQWVLYTAA HCNSRBFMRH LKGMAGHAY YDEVEEFYREE KFREPSKKEEN VITDKSMIL ELERPSVENSE HAPLIPSLPSPPGSVCRI MGWGIATTSIE ITYPDFVHCAC NINLPNSTVC REANYGLPASKTLAGVIGLQ ITCCGDDGGG PLECEGQFGQQ ELSWGSIDCPA | 28,189 Da | Central Nervous System, Ion channel | Not Yet Recruiting | Not Approved | Not available | https://pubchem.ncbi.nlm.nih.gov/compound/16129677 |
| 21    | Apamin                | Apis mellifica | CNCKAPEXALCARRCQQH | 5,223 Da | Antibiotics, Antimicrobial, Fungicide | Central Nervous System, Ion channel | Not Yet Recruiting | Not Approved | Not available | https://pubchem.ncbi.nlm.nih.gov/compound/16198717 |
| 22    | Arenicin-1            | Arenicola marina | GMCWYVYCRNGVRCYRRCN | 22,497 Da | Antibiotics, Antimicrobial, Fungicide | Completed | Approved | Prescription | https://www.uniprot.org/uniprot/Q5SC60 |
| 23    | Aurelin               | Aurelia aurita | AACSDRAHICJSFKEKEDSGRNGYKVRANCKKTCGLC | 4296.95 Da | Antibiotic, Antimicrobial | Completed | Approved | Prescription | https://pubmed.ncbi.nlm.nih.gov/16890198/ |
| 24    | Hepecidin             | Oreochromis mossambica | DTHPPFCICCCGCCHBSCGMCCKT | 2789.4 Da | Antibiotics, Antimicrobial, Fungicides, Hormone | Completed | Approved | Prescription | https://pubchem.ncbi.nlm.nih.gov/compound/16198717 |
| 25    | Scygonadin            | Scylla paramamoul | KRSLLLGLT VVVLGLVPVF PCMAGQALMN LMVPQSSIAI MVYQGGPAVNG TGLHGCYEL STRQFPAGPTT AEMCSASWTH DNPGYEGRS RBELDAKGS TNPVTQASIN YKPIFDIE EWDDSY | 13,736 Da | Antimicrobial Activity Against Gram Positive Bacterium | Ongoing | Investigation is in process | Research use only | https://www.uniprot.org/uniprot/QSG60 |
| 26    | Hyastatin             | Hyas araneus | MBBLLVLVS AALAAHEFS ELKSGYVQYG TLPFQGGQSG PHLLGGGIGG REPQPSQNLGI KRSTGRIPP FPQPGYGYSR NSCRQPCST YGGRGECR | 13,452Da | C. Glutamicum, E.Coli, S. Aureus, P. Aeruginosa | Completed | Approved | Prescription | https://pubmed.ncbi.nlm.nih.gov/16890198/ |
| 27    | Tauramamide           | Taurama hainanum | YSLWR | 864 Da | Multidrug Resistant Bacteria | Ongoing | Investigation is in process | Research use only | https://pubchem.ncbi.nlm.nih.gov/compound/16198717 |
| 28    | Centrocin 1b          | Strongylocentrotus droebachiensis | SMMKVLVLC AIVATMSVCA KNFEQD0AL TIL0NML3SE VASPIDAVAL Q04FCKHTFKH VSHAVKSDHI AQGRQCGASLG FSEPFAARV NLTAPEMKREE | 12,864 Da | Immune System | Ongoing | Not approved | Research use only | https://www.uniprot.org/uniprot/Q56710 |
| 29    | Calcisepine           | Dendroaspis polypepina | DYTQRCWVRL TKR0100VQ I0G0342Q0 LGK0100VQ 0100VQ | 7044 Da | L-Type Calcium Channel Blocker | Ongoing | Not Approved | Research use only | https://www.uniprot.org/uniprot/Q56710 |
| 30    | μ-EPTX-Na1a           | Naja arena | LKCHNTQFPHYKTCPGEGNLCKFATKLEFKLPLPKPREGCADNCPKSNLKLPHYCVCSDFTKCN | 7053.63 Da | Voltage-gated sodium channel Nav1.8 | Ongoing | Not Approved | Research use only | https://pubchem.ncbi.nlm.nih.gov/compound/30864211/ |
as gliomas (Arzamasov et al., 2014). It has been shown to block chloride channels which are expressed by the tumor glioma cells (Beeton, 2013). It was initially developed for the diagnosis and treatment of gliomas, recently it has been shown to specifically label cancer cells from solid tumors such as melanoma, small cell lung carcinoma, neuroblastoma, medulloblastoma, Ewing’s sarcoma, and pheochromocytoma (Sabatier and De Waard, 2013). In addition to chloride channels, other receptor sites such as matrix metalloproteinase-2 and Annexin-2A have also been claimed to be the binding sites for CTX (Dardevet et al., 2015).

**Centipede venom-Histamine**

The centipede Scolopendra viridicorns venom has been shown to cause a local inflammatory response in individuals by inducing edema, leukocyte recruitment, and mast cells degranulation (Távora et al., 2016). None of the centipede venom peptides have yet progressed to late-stage preclinical studies or clinical trials (Undheim et al., 2016). Histamine can be used to produce a variety of effects within the body, including the contraction of smooth muscle tissues of the lungs, uterus, and stomach; the dilation of blood vessels, this increases permeability and lowers blood pressure; the stimulation of gastric acid secretion in the stomach; and the acceleration of heart rate (Table 1).

**Marine cone snail-Conotoxin**

The venomous snail conotoxins are a valuable pharmacological probe and potential drug lead due to their highly specific nature and higher affinity towards ion channels, receptors, and transporters in the central nervous systems of target prey and humans (Gao et al., 2017). The conopeptide drug ω-conotoxin MVIIA isolated from Conus magus, has been clinically approved for the treatment of intractable pain, when directly administered to the spinal cord it specifically blocks a pain transmitting ion channel subtype called N-Type Ca2+ channels (Jin et al., 2019). Several conotoxin members have been identified with definable pharmacological families that target the neuronal tissues: α (alpha), i (iota), κ (kappa), and ρ (rho); which in turn target nicotinic acetylcholine receptors, voltage-gated Na channels, voltage-gated K channels, and α1-adrenoceptors, respectively (Sudewi et al., 2019). The other conopeptides are being evaluated for their potential antinociceptive properties and clot-dissolving cardioprotective agent (Becker and Terlau, 2008; Sousa et al., 2018).

More recently, KCP-400, which is also called RgIA4 is derived from the venom of the Conus regius, a potent antagonist of the nicotinic acetylcholine receptor (nAChR). KCP-400 has been reported in its preclinical studies to provide relief against chronic pain (Pennington et al., 2018).

**Lizard venom-Exenatide**

Exenatide is the synthetic form of a protein that mimics the action of glucagon-like peptide-1 (Table 1) which is found in the saliva of the Gila monster, shown to be important in glucose homeostasis and useful in the treatment of patients with diabetes mellitus (Truitt and Chiquette, 2006). A synthetic analogue is known as Byetta also called exendin-4; exenatide was developed as a treatment for diabetes, shown to mimic GLP-1 by stimulating the GLP-1 receptor (Furman, 2012). Exendin-4 enhanced the physiological functions of β-cells and upregulated GLP-1 receptors thereby reducing the plasma glucose levels. Exenatide has also been found to be useful in ameliorating neuropathy, nephropathy, and ventricular remodeling (Yap and Misuan, 2018).

**Leech venom-Bivalirudin**

Bivalirudin is an analogue of hirudin is used in the treatment of deep vein thrombosis and repair of coronary angioplasty (Beeton, 2013). It is a bivalent direct thrombin inhibitor that binds to two distinct sites on thrombin- the active catalytic site and fibrinogen-binding site- exosite 1 (Warren, 2004). It was found to reduce the risk of bleeding and was approved by FDA for the treatment of unstable angina undergoing percutaneous transluminal coronary angioplasty (Bordon, 2020). As its binding to thrombin is reversible, Bivalirudin after the binding, is slowly cleaved by thrombin and hence thrombin activity gets transiently inhibited later its enzymatic activity is restored (Chudzinski-Tavassi et al., 2018).

**Saw-scaled viper snake-Tirofiban**

Tirofiban is a non-peptide molecule that was the first antiplatelet drug derived from a snake venom protein is a low molecular weight reversible antagonist (Lazarovici et al., 2019). It has been shown to block the binding of fibrinogen to αIIbβ3 integrin (a fibrinogen receptor) and hence is used in the treatment of patients with unstable angina or NSTEMI who are undergoing PCI (Beeton, 2013; Lazarovici et al., 2019). Tirofiban thus reduces the risk of ischaemic complications in patients with unstable angina/non-Q-wave MI and also high-risk patients undergoing revascularisation when used against a background of heparin and aspirin, and hence can be used as an adjunct to heparin and aspirin in patients with acute coronary syndromes (McClellan and Goa, 1998).

**Honey bee venom-Apitoxin**

The bee venom apitoxins from Apis mellifera have been shown to possess antitumor activities against different types of cancer cells such as breast, liver, blood, lung, skin, and prostate cancer cells (Webbe et al., 2019). Apitoxin and its component melittin have been shown to possess potential application against oral pathogens with their antibacterial properties (Leandro et al., 2015). Apitoxin is also reviewed for its anti-inflammatory, anti-arthritis, and neuroprotective effects against Parkinson’s disease (PD), Alzheimer’s disease (AD), and amyotrophic lateral sclerosis (ALS) (Oukschaider et al., 2020). Importantly, Apitoxin® in a recent FDA phase 3 study has been implicated for the reduction of pain and increase in mobility in Osteoarthritis patients.

**Cobra venom-Cobrotoxin**

Cobrotoxins are postsynaptic neurotoxins that bind to the acetylcholine receptors on the motor endplate (Warrell, 2020). Cobrotoxin has also been shown to be a potential drug candidate for chronic kidney diseases as its administration elevated anti-inflammatory cytokine IL-10 expression; inhibited phosphorylation of IκB-α and NF-κB p65 nuclear translocation; upregulated protein levels of podocyte-specific nephrin; downregulated the level of fibrosis-related TGF-β in Adriamycin- induced chronic nephropathy in a rat model (Wang et al., 2015). It has also been proposed to possess the potential to treat patients with COVID-19 or to inhibit SARS-COV-2 infection because it can inhibit the cytokine storm caused by SARS-COV2 infection; inhibit the proliferation of CD8 T-cells more than that of CD4 T cells to restore the CD4/CD8 ratio; inhibit lung inflammation, improve lung gas exchange function, and attenuating the development of fibrotic lesions in the lung; analgesics action providing relief to patients with muscle pain and headache; antiviral activity against SARS-COV2 (Lin et al., 2020).

**Leech venom-Desirudin**

Desirudin is a recombinant analogue of hirudin which has promising anticoagulant potential approved by the FDA and is currently in use for the prevention of Deep Vein Thrombosis (DVT) following hip or knee replacement surgery (Abdualkader et al., 2011). Desirudin...
inhibits the different actions of thrombin such as fibrin formation, activation of coagulation factors V, VII, and XIII, and platelet aggregation, which results in a dose-dependent prolongation of a PTT (Koh and Kini, 2008). These are categorized under the class of Direct Thrombin Inhibitors (DTIs) which overcome the disadvantages of indirect thrombin inhibitors such as unfractionated heparins (Kong et al., 2014). It is also approved for treating heparin-induced thrombocytopenia (HIT) and for thrombotic prophylaxis following orthopedic surgery (Min et al., 2010).

**Jararaca pit viper snake venom-Enalapril**

Enalapril is an angiotensin-converting enzyme (ACE) inhibitor that is used for the treatment of hypertension, congestive heart failure, post-myocardial infarction, and other indications. Enalapril is a pneumonia ACE inhibitor that reduces the risk of pneumonia by nearly one-third when compared to antagonists against calcium channel or beta-adrenoceptor in the treatment of hypertension (Davis et al., 2007). It was shown to be orally active, long-acting, with lesser side effects because of the absence of sulphhydryl group; gets extensively hydrolyzed to its bioactive form in vivo to enalaprilat taking place in the liver (Gomez et al., 1985). In patients with congestive heart failure, administration of enalapril reduced mortality significantly by improving general signs & symptoms of left and right ventricular heart failure, reduction of heart size and blood pressure (Kjekshus and Swedberg, 1989).

**Pygmy rattle snake venom-Epitifibatide**

Epitifibatide is a glycoprotein IIb/IIIa class platelet inhibiting drug used to reduce ischemic cardiac events approved by FDA for Acute Coronary Syndrome (ACS) and Percutaneous Coronary Intervention (PCI) (Phillips and Scarborough, 1997). A rupture in the atherosclerotic plaque or endothelial injury exposes the subendothelial matrix of the coronary blood vessel to the circulating platelets which in turn triggers a signaling cascade that leads to the activation of glycoprotein IIb/IIIa receptor (GpIIb/IIIa) (Sangkuhl et al., 2011). Epitifibatide belongs to the “disintegrin” peptide family which contains the sequence Arg-Gly-Asp (RGD) and mediates their effect by blocking αIIbβ3 integrin, which are the most powerful inhibitors of platelet aggregation (Lazarovici et al., 2019). It specifically functions by blocking the binding of adhesive proteins fibrinogen and von Willebrand factor to GP IIb/IIIa on the surface of activated platelets (Scarborough, 1999).

**Gila monster lizard venom-Lixisenatide**

Lixisenatide is a 44 amino acid exendin-4-like analogue (Table 1) where it has C-terminal modification with the addition of 6 lysine residues and one proline deleted (Page, 2014). It is one of the anti-diabetic drugs which stimulate the GLP-1 receptor for binding of incretin-1 which in turn inhibits the release of glucagon, increases insulin secretion, delays gastric emptying, and is hence used for improving glycemic control in Type-2 diabetes mellitus (Brody, 2018). It also demonstrated mild improvements in HbA1c, with slightly lowered mean weight loss and better gastrointestinal tolerability with a lower incidence of hypoglycemia (Lear et al., 2019). Because of its higher CNS penetrating capability, it has also been implicated to have potential neuroprotective properties and the results have been promising at equivalent doses in in vitro models of neurodegeneration (Foltynie and Ashuda, 2020). Unfortunately, its efficacy begins to reduce once anti-lixisenatide antibodies are produced in the body as it stimulates the immune system (Brody, 2018).

**Cone snail venom-Ziconotide**

Ziconotide was the first marine-derived natural product approved by FDA in 2005 for its clinical application for neuropathic pain as a nonopioid analgesic (Shilpi and Uddin, 2020). It has been approved for the treatment of intractable cancer pain, phantom limb, chronic neuropathic pain, acute and chronic inflammatory pain and marketed as PRIALT® (Honore and Jarvis, 2007). Ziconotide targets presynaptic VGCCs (N-type voltage-gated calcium channels Ca_2.2) by binding to their α1B subunit obstructing the entry of Ca^{2+}, which blocks neurotransmitter release and thereby prevents the synaptic transmission of pain sensation (Shilpi and Uddin, 2020). By blocking the neurotransmitter release from primary nociceptive afferents it prevents the transmission of pain signals to the brain (Mari and Tytgat, 2010). Ziconotide can also act on the Ca_3.1 and Ca_3.3 subtypes of the T-type calcium channel which are expressed extensively in the thalamus & cortex, are important for the regulation of thalamocortical signaling: an important component of sleep/wake regulation; has potential neuroprotective activity against epilepsy, schizophrenia, tremor or tinnitus (Barrow and Duffy, 2010).

**Vespa tropica venom chemotactic peptides (VCPs)**

Chemotactic peptides are tridecapeptides in general with amphipathic, α-helical, linear, cationic, and C-terminal amide containing secondary structures with antimicrobial and hemolytic (Lee et al., 2016). In in vitro studies, these peptides displayed broad-spectrum antimicrobial activity against the standard and clinically isolated strains of bacteria and showed weak hemolytic activity towards human erythrocytes (Yang et al., 2013). The peptides displayed direct antimicrobial activity, enhanced the ability to attract leukocytes to the site of infection, and were also able to control inflammation in animal models (Silva et al., 2020). There were only three chemotactic peptides been reported which include Orancis-protonectin (OvDP2), EpVP6, and the one found in R. brunneum (named RbVP1 hereafter) (Lee et al., 2016). In vitro anti-tumor activities have also been studied in VCPs towards NIH:OVCA-3 and SK-OV-3 ovarian cancer cell lines at concentrations higher than 10 μM (Abd El-Wahed et al., 2021).

**Wasp venom-Mastoparan**

Mastoparan is a basic amphipilic α-helical peptide that consists of 14 amino acid residues, hydrophobic and essential amino acids, and an amino acid C-terminus (Abd El-Wahed et al., 2021). They are generally polycationic, linear tetradecapeptide amides, rich in hydrophobic residues such as leucine, isoleucine, and alanine (Palma, 2013). Mastoparans are highly reactive against the cell membranes of bacteria, fungi, and erythrocytes, as well as mast cells, which results in antimicrobial, hemolytic, and Mast Cell Degranulation (MCD) activities (Lee et al., 2016). Its other biological effects include cytotoxic effects on tumor cells such as leukemia, myeloma, and breast cancer cells; induces mitochondrial permeability and powerful transition of mitochondrial permeability in homogeneous K562 cells (Abd El-Wahed et al., 2021). Mastoparan increases the GTPase activity and the rate of nucleotide-binding of several purified GTP-binding regulatory proteins (G proteins) which in turn couples cell-surface receptors to intracellular mediators; accelerates guanosine-5′-(3-O-thiotriphosphate) binding as a result of which G protein activation takes place in part by promoting the dissociation of bound GDP, (the mechanism by which receptors regulate G proteins) leading to cell toxicity (Hipshijima et al., 1988). The specific effect of MCD depends on particular cell types such as the secretion of histamine if the cells are mast cells; serotonin if the cell type is platelets; catecholamines if the cell type are chromaffin cells; prolactin from the anterior pituitary, and even insulin if the cell type is pancreatic β-cells (Lee et al., 2016). Mastoparan B and Mastoparan M are other homologues isolated from other vespid venoms which
varying their antibacterial and anti-inflammatory properties (Abd El-Wahed et al., 2021).

**Brazilian wasp venom-Protonectin**

Protonectin is a polyfunctional peptide that causes mast cell degranulation, releases lactate dehydrogenase (LDH) from mast cells, antibiotic activity against Gram-positive and Gram-negative bacteria, and chemotactic response for polymorphonucleated leukocytes (PMNL) (Baptista-Saidenberg et al., 2010). It has been shown potent antifungal activity and fungicidal activity against the candida fungi cells where its action involved disrupting membrane integrity and inducing the production of cellular ROS (Wang et al., 2015). Its antibacterial activity is due to the formation of typical α-helical conformation in a membrane-mimicking environment, studied using molecular dynamics simulations (Wang et al., 2013). Protonectin also has a significant impact on lung cancer cells A549 and healthy lung fibroblast cells where it mediated the down-regulation of BMI-1 gene expression of cancer markers and up-regulation of the production of reactive oxygen species (ROS) (Eskandari et al., 2020).

**Oreochromis mossambicus venom-Ornithine**

L-ornithine is a non-protein amino acid that is widely used to enhance human health as it has been reported to possess beneficial effects on the liver and the heart (Wu et al., 2020). Ornithine is formed mainly from L-glutamate in plants and synthesized from the urea cycle in animals as a result of the reaction catalyzed by enzymes in arginine (Seneca., 2007). L-Ornithine-L-Aspartate (LOLA) has been shown to promote hepatic ureagenesis and glutamine synthetase activity; also it promotes glutamine synthesis and possibly protein anabolism in skeletal muscle (Bajaj, 2012). Its ability to increase the buffering of ammonia during and after exercise is useful against skeletal muscle fatigue (Demura et al., 2010).

**Chinese bird spider-Hainantoxin**

Hainantoxin-I is a novel peptide toxin (Table 1), isolated from the Chinese bird spider Selenocosmia hainana venom which has 33 amino acid residues with a disulfide linkage of I-IV, II-V & III-VI, assigned by partial reduction and sequence analysis (Li et al., 2004). The intermediate-conductance CaV3-activated K+ (IK) channels (calcium/caldulin-regulated voltage-independent K+ channels), whose activation (activation of IK currents) is important in blood vessels and respiratory tissues is mediated by hainantoxin-I (HNTX-I) as an IK-channel activator with little effect on voltage-gated Na+ and Ca2+ channels studied in rat dorsal root ganglion neurons and also the heterologous expression of voltage-gated rapidly activating delayed rectifier K+ channels in HEK293T cells (Huang et al., 2014). Hainantoxin-II (HnTx-II), is another neurotoxin isolated from the venom of the Chinese bird spider (Haploplema hainanum) has higher insecticidal activity and lower lethalic activity on mammals (Pan and Yu, 2010). Hainantoxin-III is a selective antagonist of neuronal tetrodotoxin-sensitive voltage-gated sodium channels; wherein it suppresses Nav1.7 current amplitude without altering any activation, inactivation, and repriming kinetics (Liu et al., 2015). Hainantoxin-IV (HNTX-IV) can specifically inhibit the neuronal tetrodotoxin-sensitive sodium channels and interact with neurotoxin receptor site 1 via a similar mechanism to that of TTX without affecting the activation and inactivation kinetics (Li et al., 2004). Hainantoxin-V is also a neurotoxic peptide that inhibits the tetrodotoxin-sensitive (TTX-S) sodium currents without any effects on tetrodotoxin-resistant (TTX-R) sodium currents on adult rats dorsal root ganglion neurons (Xiao and Liang, 2005).

**Tarantula venom peptides**

*Theraphosa apophysis* venom has been recently reported to possess two tarantula-venom peptides (Tap1a and Tap2a). They have been identified to modulate the activity of both NaV and CaV3 channels. Inhibition of NaV and CaV3 channels by Tap1a and Tap2a has been identified as their mode of action in relieving from chronic visceral pain in a model of irritable bowel syndrome (Cardoso et al., 2021).

**Batroxobin**

Batroxobin is a serine protease toxin (SVSP) isolated from the venom of many species of pit viper snakes. Batroxobin is an enzyme protein synthesized as a pre-proenzyme containing 18 residues pre-peptide with a six residue pro-peptide (Table 1) and has its clinical use as a defibrinogenating agent for various clinical conditions such as deep vein thrombosis, myocardial infarction, pulmonary embolus, central retinal vein occlusion, peripheral vascular disease, acute ischemic stroke, angina pectoris, glomerulonephritis, priapism, sickle cell crises and renal transplant rejection (Markland and Swenson, 2013). Batroxobin can boost the plasma plasmin concentration by inducing the release of plasminogen activator from the vascular endothelial cells and activate the fibrinolytic response which leads to the production of soluble non-functional fibrin degradation products and remove them from the plasma (Kaur et al., 2012). It effectively releases the fibrinopeptide A by cleaving the a-chain of fibrinogen (Slagboom et al., 2017). It inhibits human neutrophil extracellular traps (NETs) induced by tumor necrosis factor-α (TNF-α) in the presence of human fibrinogen and protects against severe ischemic tissue injury and accelerates vascular and skeletal muscle regeneration (Masuda et al., 2019).

**Bee venom toxin-Apamin**

Apamin is a neurotoxin peptide containing 18 amino acid residues which are tightly cross-linked by two disulfide bonds; mediates its pharmacological functions by irreversibly blocking CaV2.3-activated K+ (SK) channels; also regulates gene expression of many signal transduction pathways involving cell development (Gu et al., 2020). Apamin specifically can block the CaV2.3-activated potassium permeability which results from receptor activation (Strong and Brewer, 1992). As it is permeable to the blood–brain barrier, it can cause its effects on the CNS by different routes of administration; when peripherally applied it selectively and potently affects the K+ permeability of certain membranes such as smooth muscle of the gut (Palma, 2013). During this phase, there is a fall in the delayed hyperpolarization of cells, which can result in the elevated continuous firing of neurons in the mesencephalon and cerebellum which in turn elevates the cell sensitivity to excitatory inputs (Pucca et al., 2019). Apamin can activate the inhibitory muscarinic receptors of motor nerve terminals causing reduced neuromuscular transmission, which is undergoing experimental validation for potential treatment against diseases that present high muscle excitability, such as Parkinson’s disease, learning deficit disorder, and other disabilities (Pucca et al., 2019).

**Polychaeate: Arenicola marina venom-Arenicin-1**

Arenicin-1 is a β-sheet antimicrobial peptide isolated from a marine polychaeta Arenicola marina a type of coelomocytes that has a potent, broad-spectrum antimicrobial activity (Orlov et al., 2019). It is a 21-residue peptide acting against pathogenic fungi by disrupting phospholipid membranes (Park and Lee, 2009). In studies done on Candida spp., there was an increase in the production of ROS and cytotoxic hydroxyl radicals production which lead to apoptosis due to mitochondrial dysfunction caused by arenicin-1 induced membrane depolarization and release of activated metacaspases (Cho and Lee, 2011).
further initiated apoptotic mechanism by causing plasma membrane depolarization; exposing the phosphatidylycerine towards the outer surface; morphological changes in the nucleus and DNA structure (Cho and Lee, 2011). Based on these findings it is clear that arenicin-1 is a potent antifungal agent that primarily acts by inducing apoptosis. It also possesses antibacterial activity and displays hemolytic activity against human red blood cells (Lee et al., 2008).

**Jelly fish toxin-Aurelin**

Aurelin is a novel antimicrobial peptide made up of 40 amino acids (Table 1) that has been shown to exhibit antibacterial activity against gram-positive and gram-negative bacteria (Ovchinnikova et al., 2006). It was purified from the mesogloea of a scaphoid jellyfish *Aurelia aurita* using preparative gel electrophoresis and RP-HPLC. It is initially synthesized as an 84-residue pro-pre-aurelin consisting of a 22-residue putative signal peptide and a pro-stretch of 22 residues. It has no structural homology with any of the previously identified antimicrobial peptides but has partial similarity to defensins and K+ channel-blocking toxins of sea anemones belonging to ShKT domain family (Ovchinnikova et al., 2006). A recombinant peptide with (sup 15)N-labeled analogue was produced by overexpression in *Escherichia coli*, which was purified also had modest antibacterial properties and membrane activities (Shenkarev et al., 2012).

**Oreochromis mossambicus venom-Hepcidin**

Hepcidsins are important antimicrobial peptides that resist pathogenic infections consist of 88–91 amino acid residues which vary across the three different forms (Huang et al., 2007). They were isolated from tilapia (*Oreochromis mossambicus*), and named TH1-5, TH2-2, and TH2-3 based on their sequence composition through hybridization of phage library; further synthetic peptides were also isolated and named as TH-1 and TH-2 which are also shown to have antimicrobial properties (Huang et al., 2007). Tilapia hepcidin (TH)1-5, has been also shown to induce an inflammatory response in HeLa cells indicating its potential application for cancer therapy (Chang et al., 2011). TH-1-5 was found to be cytotoxic against MCF7 indicating it to be a promising cytotoxic peptide that warrants further studies as a potential anticancer agent for the treatment of breast cancer (Al-kassim Hassan et al., 2015). It was found to activate caspases-3/7 and –9; suggesting induction of apoptosis via the intrinsic pathway providing further evidence for potential agent treatment breast cancer (Hassan et al., 2016).

**Scylla serrata venom-Scygonadin**

Scygonadin comprises 102 amino acids (Table 1) with a theoretical molecular weight of 11.272 kDa having strong implications in providing reproductive immunity found generally in the seminal plasma of the mud crab, *Scylla serrata* (Li, 2013). It is an antimicrobial offers protection against microorganisms due to its anionic group, pl 6.0, antibacterial activity against *A. hydrophila* (G-) and *M. leteus* (G+) (Wang et al., 2006). Its 126 amino acids sequence constitutes a putative NH (2)-terminal signal sequence of 1–24 and a mature peptide 25–126 sequence (Wang et al., 2007). *P. pastoris*-derived recombinant scygonadin demonstrated a higher antimicrobial activity against pathogenic *Aeromonas hydrophila* showing salt-resistance and time-dependent killing kinetics; also antiviral potential demonstrating interference with replication of white spot syndrome virus (WSSV) in in vitro-cultured crayfish haemato poetic (Hpt) cells (Peng et al., 2012). The mature peptide expressed in *Escherichia coli* has an approximately 43 kDa fusion protein CKS-scygonadin was found to be highly stable, soluble, active against both Gram-positive and Gram-negative bacteria showing its antibacterial properties (Peng et al., 2010).

**Hyas araneus venom-Hyastatin**

Hyastatin is an 11.7 kDa (Table 1) Gly-rich peptide isolated from the hemocytes of the spider crab *Hyas araneus* (Kang et al., 2015). It is made up of three distinct domains: N-terminal region rich in Glycine residues, short Proline or Arginine-rich region, and C-terminal region with six Cysteine residues resembling the one found in penaeidins; have shown antimicrobial properties against yeasts, and Gram-positive and Gram-negative bacteria (Sperstad et al., 2009). A recombinant product of Sp Hyastatin (from *Scylla paramamosain*) showed potent antimicrobial activity against *Staphylococcus aureus, Aeromonas hydrophila, and Pseudomonas fluorescens* with antimicrobial mechanism attributing to the ability to disrupt cell membrane integrity on Hyastatin treatment (Shan et al., 2016). As both native hyastatin and its N-terminus region can bind chitin, this may facilitate antifungal capability whereas its antibacterial properties can be attributed to the cysteine-rich C-terminus domain, since it is absent in the recombinant hyastatin which do not possess antibacterial properties (Smith et al., 2010).

**Brevibacillus laterosporus protein-Tauramamide**

Tauramamide is a novel lipopeptide antibiotic produced by the culture of marine bacterial isolate *Brevibacillus laterosporus* PNG276 (Hassi et al., 2012). It is a linear lipopeptide that is made up of 7-methyloctanoic acid esterified on a pentapeptide chain (Yang et al., 2016). Tauramamide and its ethyl ester showed potent antibiotic activity against pathogenic *Enterococcus sp.* (Desjardine et al., 2007), it is made up of two D-amino acids with an acylated N-terminus (Debbab et al., 2010). Antimicrobial peptides, tauramamide, ethyl ester, thiopeptides, and depsipeptides, from marine bacterial origin showed effective inhibition of human pathogenic *Enterococcus sp* (Biswas et al., 2016).

**Strongylocentrotus droebachiensis venom-Centrocins**

Venom from the green sea urchin *Strongylocentrotus droebachiensis*, centrocins 1 and 2 were purified from the coelomocyte extracts (Li et al., 2010). The centrocins possess an intramolecular heterodimeric structure with a heavy chain made up of 30 amino acids and a light chain made up of 12 amino acids (Björn et al., 2012). The full-length sequence of centrocin 1 is made up of 119 amino acids, whereas centrocin 2 is made up of 118 amino acids which both include a pre-sequence consisting of 51 or 50 amino acids for centrocins 1 and 2, respectively, with 24 amino acids inter-chain between the heavy and light chain (Li et al., 2010). The nature of native peptides is cationic and showed potent activity against Gram-positive and Gram-negative bacteria. The synthesis and subsequent antimicrobial testing of individual monomers have shown that the cationic containing heavy chain and the original dimeric peptide are equally active which showed a broad spectrum antimicrobial property, resistance to physiological salt concentration, and anti-inflammatory properties (Björn et al., 2012). It was further demonstrated that centrocin 1 was produced by phagocytes, stored in granular vesicles which co-localizes with phagocytosed bacteria suggesting the formation of phagolysosomes for its microbicidal action (Li et al., 2010).

**Black mamba venom-Calci septine**

Calci septine is the venom peptide of black mamba which is made up of 60-amino acids with four disulphide bonds (Garcia et al., 2001). It is a smooth muscle relaxant and a cardiac contraction inhibitor with its physiological actions similar to that of 1,4-dihydropyridines drugs which are important for cardiovascular disease treatment (de Weille et al., 1991). It selectively blocks the L-type Ca2+...
channels and does not affect the N-type and T-type Ca\(^{2+}\) channels. It also acts as a channel agonist in skeletal muscle by modulating the permeation of divergent cations through L-type channels (García et al., 2001). It may bind to L-type Ca + channels, via the recognition site for 1, 4-dihydropyridines and hence do not affect the N-type or T-type Ca\(^{2+}\) channels (Harvey, 2013). The synthetic Calciceptine (GaS) has also shown inhibitory effects on the voltage-dependent Ca\(^{2+}\) current conductances of 25-pS and 12-pS channels in porcine tissue by reducing the mean open time and channel availability which resulted in decreased open probability of the 25-pS and 12-pS channels with different sensitivities (Teramoto et al., 1996).

Following are some noteworthy outcomes of venom peptide in pain management therapies.

- \(\mu\)-EPTX-Na1a, a 62-residue three-finger peptide from the venom of the Chinese cobra (Naja atra), was shown to be a potent inhibitor of the voltage-gated sodium channel Nav1.8, that exhibits a high selectivity over other voltage-gated sodium channel subtypes and hence contributing to reducing inflammatory and neuropathic pain (Zhang et al., 2019).
- Crotalaphine- a crotalid venom that is isolated and has been chemically characterized as a novel and potent antinociceptive peptide is responsible for the oral opioid activity that induced antinociception which was mediated via activation of kappa-opioid receptors (Konno et al., 2008).
- Buthus martensii (Karsch)- an analgesic-antitumor peptide (BmK AGAP) – is isolated from scorpion venom peptide that mediates analgesic properties by inhibiting the neuropathic and inflammation-associated pain through a MAPK-mediated mechanism (Ruan et al., 2018).
- PnPP-19- isolated from spider Phoneutria nigrivenator was shown to induce central antinociception that involves the activation of CB1 cannabinoid, \(\mu\)- and \(\delta\)-opioid receptors (da Fonseca Pacheco et al., 2016).
- Apitox® in a recent FDA Phase 3 study has been implicated for the reduction of pain and increase in mobility to Osteoarthritis patients.
- KCP-400 (Rgl4A) has been reported in its preclinical studies to provide relief against chronic pain relief (Pennington et al., 2018). Furthermore, research and drug development are in progress.

Conclusion

Venoms are a rich source of novel compounds. Peptides of venoms of spiders, scorpions, cone snails, and especially snakes have been identified to physiologically play a role in protection and predation strategies of the organism. Their role in inhibiting the fast synaptic transmission have attracted researchers to choose them as plausible candidates in analgesic development. Venoms with exquisite potency and selectivity have been developed over millions of years of evolution, and we now have the means to maximise their potential.

Venom-based painkiller, which resembles the venom of cone snails, is commercially accessible. Sea anemone, spider, and scorpion venom proteins have also been discovered with potential biomedical antinociceptive use. Many notable advances have increased our understanding of venoms and its role in pain since the latter half of the twentieth century. The orientation of research in venom toxins to therapeutics has been changed phenomenally and more pain management strategies are being developed. Strategies and mechanisms established with the likes of developed therapies viz., Apitox®, PRIALT®, Crotalaphine, KCP-400 can be extended with the advent of ‘omics’ tools and synthetic chemistry in this golden age of biological drug discovery, especially for pain research.
Yap, M.K.K., Misuan, N., 2018. Exendin-4 from Heloderma suspectum venom: From Natural venom to a Therapeutic Drug. J. Am. Pharm. Assoc. 46, 74–80.

Triplitt, C., Chiquette, E., 2006. Exenatide: From the Gila Monster to the Pharmacy. J. Am. Pharm. Assoc. 46, 1149–1154.

Thobois, S., Brefel-Courbon, C., Le Bars, D., and Sgambato-Faure, V. (2018) Molecular Imaging of Opioid System in Idiopathic Parkinson’s Disease, In International Review of Neurobiology pp 275-303, Elsevier.

Hossein, M.S., Gai, S.H., Sabatier, J.-M., De Waard, M., 2015. Chlorotoxin and related peptides: Short insect toxins from scorpion venom. Russ. J. Bioorg. Chem. 40, 3482–3490.

Ceremuga, M., Stela, M., Janik, E., Gorniak, L., Synowiec, E., Sliwinski, T., Sitarek, P., Taler, S., and Sliwski, J. (2017) Neotropical Social Wasp Agelaia pallipes pallipes. Toxicon 56, 880–889.

Wang, S.-Z., Xu, Y.-L., Zhu, Q., Kou, J.-Q., Qin, Z.-H., 2015. Cobrotoxin from Naja atra Sterletti Venom Inhibits Acetylcholinesterase and Amyloid Beta Peptide (A β25-35) Deposition in vitro. J. Am. Pharm. Assoc. 339–340.

Feather, S., and D’Onofrio, D. (2016) From Animal Poisons and Venoms to Medicines: A Natural Peptide from Bee Venom Which A Natural Peptide from Bee Venom Which A Natural Peptide from Bee Venom Which A Natural Peptide from Bee Venom Which Is a Selective Inhibitor of Mast Cell Chemotaxis. Biophysica Acta (BBA) - Biomembranes 1848, 2365–2373.

Raffaeli, W., Arnaudo, E., 2017. Pain as a disease: an overview. J. Pain Res. 10, 1093–1104.

Plosker, G.L., McTavish, D., 1995. Captopril. Drugs Aging 7, 226–235.

Gomez, H.J., Cirillo, V.J., Irvin, J.D., 1985. Enalapril. Davis, S., 2007. Enalapril. In: Enna, S.J., Bylund, D.B. (Eds.), xPharm: The Comprehensive Pharmacology Reference. Elsevier, New York, pp. 1–6.

Cortelli, P., Giannini, G., Favoni, V., Cevoli, S., Pierangeli, G., 2013. Nociception and the regulation of pain. Neurological Society and of the Italian Society of Clinical Neurophysiology 34, 7–15.

Ceremuga, M., Stela, M., Janik, E., Gorniak, L., Synowiec, E., Sliwinski, T., Sitarek, P., Taler, S., and Sliwski, J. (2017) Neotropical Social Wasp Agelaia pallipes pallipes. Toxicon 56, 880–889.

Rabinovich, M., Almeida, C., and Trefzer, C. H. G, 2015. Antimicrobial activity of venom components from the social wasp Agelaia pallipes. Toxicon 98, 89-100.

Fischer, S., Kapp, K., Brzezinski, L., and Dziewiatkowski, P. (2014) Inhibition of intercellular beta-secretase (BACE-1) and tau protein phosphorylation by snake venoms. Frontiers in Pharmacology 5, 126.

Levchenko, A., Bashmakova, E., and Kiseleva, V. (2013) Herpes Simplex Virus type 1 (HSV-1) is a novel beta-secretase (BACE-1) substrate. PLoS One 8, e67555.

Dubey, R., and Bala, R., 2010. Membrane effects of melittin on gastric and colorectal cancer. PLoS ONE 14, e0224028.

Ceremuga, M., Stela, M., Janik, E., Gorniak, L., Synowiec, E., Sliwinski, T., Sitarek, P., Taler, S., and Sliwski, J. (2017) Neotropical Social Wasp Agelaia pallipes pallipes. Toxicon 56, 880–889.

Lee, S., Kim, Y., Kwon, K., Lee, H.K., Oh, W., and Kwon, M., 2020. Identification of a novel chemotactic peptide from the venom of the social wasp A. pallipes. Biochem. Biophys. Acta (BBA) - Bioenergetics 1848, 2365–2373.

Warrell, D.A., 2020. Animals Hazardous to Humans. In: Human’s Tropical Medicine and Emerging Infectious Diseases pp. Elsevier, pp. 966–987.

Sangkhia, K., Shulinder, A.R., Klein, T.E., Albam, R.B., 2011. Platelet aggregation pathway. Pharmacogenet. Genomics. 21, 516–521.

Shi, J., Yuan, S.-Z., Xu, Y.-L., Zhu, Q., Kou, J.-Q., Qin, Z.-H., 2015. Melittin, a honeybee venom-derived antimicrobial peptide, may target methicillin-resistant Staphylococcus aureus. Mol. Med. Rep. 12, 6483–6490.

Yam, M., Loh, Y., Tan, C., Khadijah Adam, S., Abdul Manan, N., Basir, R., 2018. General Venom and melittin suppress growth factor receptor activation in HER2-enriched breast cancer. Toxicon 121, 51–59.

Carvalho, M. C. F., Cologna, C. T., Fornari-Baldo, E. C., Pinheiro-Júnior, E. L., Cerni, F. A., and Ribeiro, S. L. (2019) Invertebrate α-Defensins: a Mini-Review. Molecules (Basel, Switzerland) 24, 2778–2794.

Bordon, K.D. C. F., Cologna, C. T., Fornari-Baldo, E. C., Pinheiro-Júnior, E. L., Cerni, F. A., and Ribeiro, S. L. (2019) Invertebrate α-Defensins: a Mini-Review. Molecules (Basel, Switzerland) 24, 2778–2794.

Davis, S., 2007. Enalapril. In: Enna, S.J., Bylund, D.B. (Eds.), xPharm: The Comprehensive Pharmacology Reference. Elsevier, New York, pp. 1–6.

Ames, S., 2018. Antioxidant activity of selenite in vitro. J. Biol. Chem. 40, 3482–3489.

Fischer, S., Kapp, K., Brzezinski, L., and Dziewiatkowski, P. (2014) Inhibition of intercellular beta-secretase (BACE-1) and tau protein phosphorylation by snake venoms. Frontiers in Pharmacology 5, 126.

Dubey, R., and Bala, R., 2010. Membrane effects of melittin on gastric and colorectal cancer. PLoS ONE 14, e0224028.

Thobois, S., Brefel-Courbon, C., Le Bars, D., and Sgambato-Faure, V. (2018) Molecular Imaging of Opioid System in Idiopathic Parkinson’s Disease, In International Review of Neurobiology pp 275-303, Elsevier.

Hossein, M.S., Gai, S.H., Sabatier, J.-M., De Waard, M., 2015. Chlorotoxin and related peptides: Short insect toxins from scorpion venom. Russ. J. Bioorg. Chem. 40, 3482–3490.

Ceremuga, M., Stela, M., Janik, E., Gorniak, L., Synowiec, E., Sliwinski, T., Sitarek, P., Taler, S., and Sliwski, J. (2017) Neotropical Social Wasp Agelaia pallipes pallipes. Toxicon 56, 880–889.

Wang, S.-Z., Xu, Y.-L., Zhu, Q., Kou, J.-Q., Qin, Z.-H., 2015. Cobrotoxin from Naja atra Sterletti Venom Inhibits Acetylcholinesterase and Amyloid Beta Peptide (A β25-35) Deposition in vitro. J. Am. Pharm. Assoc. 339–340.

Leandro, L.F., Mendes, C.A., Casemiro, L.A., Vinholtis, A.H.C., Cunha, W.R., Almeida, R., and Martins, C. H. G. 2015. Antimicrobial activity of apitoxin, melittin and phospholipase A2 of honey bee melittin (Apis mellifera) venom against oral pathogens. Anais da Academia Brasileira de Ciências 87, 147–155.

Apostolou, A., Hafner, P., Khan, S., El-Sayed, M., Böttner, S., 2020. Apitoxin and Its Components Against Cancer, Neurodegeneration and Neuroinflammation. Limitation and Possibilities. Toxins 12, 66.

Warrell, D.A., 2020. Animals Hazardous to Humans. In: Human’s Tropical Medicine and Emerging Infectious Diseases pp. Elsevier, pp. 966–987.

Wang, S.-Z., Xu, Y.-L., Zhu, Q., Kou, J.-Q., Qin, Z.-H., 2015. Cobrotoxin from Naja atra Sterletti Venom Inhibits Acetylcholinesterase and Amyloid Beta Peptide (A β25-35) Deposition in vitro. J. Am. Pharm. Assoc. 339–340.

Leandro, L.F., Mendes, C.A., Casemiro, L.A., Vinholtis, A.H.C., Cunha, W.R., Almeida, R., and Martins, C. H. G. 2015. Antimicrobial activity of apitoxin, melittin and phospholipase A2 of honey bee melittin (Apis mellifera) venom against oral pathogens. Anais da Academia Brasileira de Ciências 87, 147–155.

V. V et al. Current Research in Toxicology 2 (2021) 329-340

V. V et al. Current Research in Toxicology 2 (2021) 329-340
V. V. et al. Current Research in Toxicology 2 (2021) 329-340

Eskandari, R., Asodeh, A., Behnam-Rassouli, F., 2020. The Therapeutic Effects of an Antimicrobial Peptide Proteotion (II-159) on A549 Cancer Cell Line. Int. J. Pept. Res. Ther. 27, 679–682.

Wu, X.-Y., Guo, X.-Y., Zhang, B., Jiang, Y., Ye, B.-C., 2020. Recent Advances of L-ornithine Biosynthesis in Metabolically Engineered Corynebacterium glutamicum. Frontiers in Bioengineering and Biotechnology 7.

Scriabine, V. et al. (2007) Alkaloids Chemistry, In Alkaloids - Secrets of Life pp 61-139, Elsevier.

Bajaj, J.S. (2012) Hepatic Encephalopathy, In Zakim and Boyer’s Hepatology pp 267-270.

Huang, P.-H., Chen, J.-Y., Kuo, C.-M., 2007. Three different hepcidins from tilapia, Ovchinnikova, T.V., Balandin, S.V., Aleshina, G.M., Tagaev, A.A., Leonova, Y.F., 2005. Cytotoxic effects of hepcidin (th1-5) on human breast cancer cell line (MCF7). Jurnal Teknologi 77, 85-90.

Al-kasim Hassan, M., Azem-A., Dharbarani, S., Mohd, K.S., 2015. Cytotoxic effect of hepcidin (th1-5) on human breast cancer cell line (MCF7). Jurnal Teknologi 77.

Shan, Z., Xu, Z., Peng, H., Chen, B., Liu, J., Chen, F., Ma, X., Wang, S., Qiao, and W., 2016. The New Antimicrobial Peptide Sphlyastatin from the Mud Crab Scylla paramamosain with Multiple Antimicrobial Mechanisms and High Effect on Bacterial Infection. Frontiers in Immunology 7.

Arenicola marina, by Strand Rearrangement or Branching, Substitution of Specific Residues, and Backbone Linearization or Cyclization. Mar. Drugs 17, 37634.

Huang, P., Zhang, Y., Chen, X., Zhou, L., Yin, D., Zeng, X., Liang, S., 2014. The Activation Effect of Hainantoxin-I, a Peptide Toxin from the Chinese Spider, Orithonoctus hainana, on Intermediate-Conductance Ca2+–Activated K+ Channels. Toxins 6, 2568-2579.

Pan, J.Y., Yu, Z.Q., 2010. Isolation and characterization of Hainantoxin-II, a new neurotoxic peptide from the Chinese bird spider (Haplopelma hainanense). Dongwuxue Yanjiu 31, 570–574.

Zhi, C., Liu, T., Qu, D., Meng, M., Li, J., Zou, X., Zhang, F., Li, D., Li, J., Li, Y., Hu, W., Liang, S., 2013. Structure and Function of Hainantoxin-III, a Selective Antagonist of N-type Voltage-gated Sodium Channels Isolated from the Chinese Bird Spider Orithonoctus hainana. J. Biol. Chem. 288, 20932–20943.

Xiao, Y.-C., Liang, S.-P., 2003. Purification and characterization of Hainantoxin-V, a tetrameric neurotoxin sodium inhibitor from the venom of the spider, Selenocosmia hainana. Toxicon 41, 643–650.

Cardoso, F.C., Castro, J., Grundy, L., Schober, G., Garcia-Caraballo, S., Zhao, T., Herzog, V., G.F., Brierley, S.M., Lewis, R.J., 2021. A spider venom peptide with multivalent activity on cytoskeleton and calcium channels alleviates chronic visceral pain in a model of irritable bowel syndrome. Pain 162, 569–581.

Markland, F.S., Swenson, S. (2013) Venombin A, In: Handbook of Proteolytic Enzymes pp 2025-2034, Elsevier.

Kaur, P., Gharbi, Y., Yeo, K.S., Tan, H.Z., Tan, J.C.S., Armugam, A., Strong, P.N., and Markland, F.S., Swenson, S. (2013) Venombin A, In: Handbook of Proteolytic Enzymes pp 2025-2034, Elsevier.

García, M.C., Hernández-Gallegos, Z., Escamilla, J., Sánchez, J.A., 2001. Calciseptine, a calcium channel blocker of the L-type voltage-gated calcium channel isolated from the green sea urchin, Strongylocentrotus droebachiensis. J. Membr. Biol. 184, 12134.

Biswas, K., Paul, D., Sinha, S.N., 2016. Marine bacteria: a potential tool for antibacterial peptide discovery. Biochem. Biophys. Res. Commun. 348, 1522-1526.

Watanabe, T.X., Kitamura, K., 1996. Effects of calciseptine on unitary barium channel activity in a murine ischemic hindlimb model. PLoS ONE 14, 959.

Liu, Z., Peng, H., Yang, M., Huang, W.-S., Ding, J., Qu, H.-D., Cai, J.-J., Zhang, N., Wang, K.-J., 2013. Structure and Function of Hainantoxin-III, a Selective Antagonist of N-type Voltage-gated Sodium Channels Isolated from the Chinese Bird Spider Orithonoctus hainana. J. Biol. Chem. 288, 20932–20943.

Chen, J., Wang, C., Lee, D.G. (2009) Fungicidal effect of antimicrobial peptide arenicin-1. ONE 14, 65-74.

Ahmadi, S., Barbosa, J. E., and Laustsen, A. H. (2019) Bee Updated: Current Knowledge on Bee Venom and Bee Envenoming Therapy. Frontiers in Immunology 7.

Strong, P.N., Brewster, B.S. (1992) Apamin: A Probe for Small-Conductance, Calcium-activated, Potassium Channel. Science 255, 941-943.

Seneca. (2007) Alkaloid Chemistry, In Alkaloids - Secrets of Life pp 61-139, Elsevier.

Lee, J.-U., Park, K., Lee, J.-Y., Kim, J.-K., Shin, S., Park, Y., Yahm, K., Kim, Y., 2008. Cell Selectivity of Arenicin-I and Its Derivative with Two Disulfide Bonds. Bulletin of The Korean Chemical Society 29, 1190–1194.

Ovchinnikova, T.V., Balandin, S.V., Aleshina, G.M., Tagaev, A.A., Leonova, Y.F., 2005. Arelin, a novel antimicrobial peptide from jellyfish Auralia aurita with structural features of defensins and channel-blocking toxins. Biochem. Biophys. Res. Commun. 348, 514–523.

Shenkarev, Z.O., Pantelev, P.V., Balandin, S.V., Giatuzilina, A.K., Altukhov, D.A., Finkina, E.I., Kokyakov, V.N., Arseniev, A.S., Ovchinnikova, T.V., 2012. Reconstructing and improving solution structure of antimicrobial peptide arenicin from jellyfish Auralia aurita. Biochem. Biophys. Res. Comm. 429, 63–69.

Huang, P.-H., Chen, J.-Y., Kuo, C.-M., 2007. Three different hepcidins from tilapia, Ovchinnikova, T.V., Balandin, S.V., Aleshina, G.M., Tagaev, A.A., Leonova, Y.F., 2005. Cytotoxic effects of hepcidin (th1-5) on human breast cancer cell line (MCF7). Jurnal Teknologi 77, 85-90.

Chen, J.-Y., Kuo, C.-M., 2007. Three different hepcidins from tilapia, Ovchinnikova, T.V., Balandin, S.V., Aleshina, G.M., Tagaev, A.A., Leonova, Y.F., 2005. Cytotoxic effects of hepcidin (th1-5) on human breast cancer cell line (MCF7). Jurnal Teknologi 77, 85-90.