



UNIVERSITY  
OF WOLLONGONG  
AUSTRALIA

University of Wollongong  
**Research Online**

---

Illawarra Health and Medical Research Institute

Faculty of Science, Medicine and Health

---

2016

# Scorpine-like peptides

Karen S. Luna Ramirez

*Fraunhofer Institute for Molecular Biology and Applied Ecology, ramirezsk@uow.edu.au*

Juana María Jimenez-Vargas

*Universidad Nacional Autonoma de Mexico*

Lourival D. Possani

*Universidad Nacional Autonoma de Mexico*

---

## Publication Details

Luna-Ramirez, K., Jimenez-Vargas, J. & Possani, L. D. (2016). Scorpine-like peptides. *Single Cell Biology*, 5 (2), 1000138-1-1000138-3.

Research Online is the open access institutional repository for the University of Wollongong. For further information contact the UOW Library:  
[research-pubs@uow.edu.au](mailto:research-pubs@uow.edu.au)

---

# Scorpine-like peptides

## Abstract

Scorpine-like peptides are intriguing and unique compounds of scorpion venom. They possess two well-defined regions that confers them bi-functionality. The N-terminal region is similar to scorpion antimicrobial peptides lacking disulfide bridges, whereas the C-terminal region contains six cysteines forming three disulfide bridges that tightly bind the peptide. Scorpine-like peptides have shown activity against bacteria (i.e. *B. subtilis*, *K. pneumoniae*, *P. aeruginosa*), fungi and also as potassium channel blockers. Additionally, they have been successful in controlling malaria and some types of viruses.

## Keywords

peptides, scorpine-like

## Disciplines

Medicine and Health Sciences

## Publication Details

Luna-Ramirez, K., Jimenez-Vargas, J. & Possani, L. D. (2016). Scorpine-like peptides. *Single Cell Biology*, 5 (2), 1000138-1-1000138-3.

Mini Review

Open Access

# Scorpine-Like Peptides

Karen Luna-Ramírez<sup>1</sup>, Juana Maria Jiménez-Vargas<sup>2</sup> and Lourival D Possani<sup>1,2\*</sup>

<sup>1</sup>Department of Bioresources, Fraunhofer Institute for Molecular Biology and Applied Ecology, Winchester Str. 2, 35394 Giessen, Germany

<sup>2</sup>Departamento de Medicina Molecular y Bioprocesos, Instituto de Biotecnología, Universidad Nacional Autónoma de México, Cuernavaca 62210, México

## Abstract

Scorpine-like peptides are intriguing and unique compounds of scorpion venom. They possess two well-defined regions that confers them bi-functionality. The N-terminal region is similar to scorpion antimicrobial peptides lacking disulfide bridges, whereas the C-terminal region contains six cysteines forming three disulfide bridges that tightly bind the peptide. Scorpine-like peptides have shown activity against bacteria (i.e. *B. subtilis*, *K. pneumoniae*, *P. aeruginosa*), fungi and also as potassium channel blockers. Additionally, they have been successful in controlling malaria and some types of viruses.

**Keywords:** Scorpion venom; Peptides; Amino acids; Antimalarial activity

## Introduction

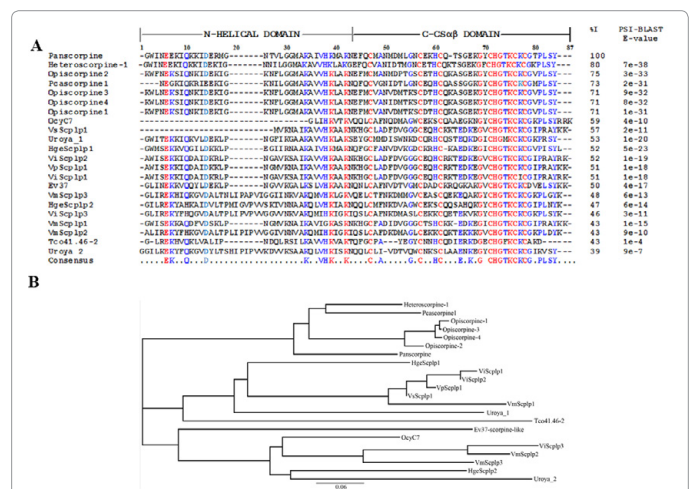
Scorpion venoms are complex mixture of peptides with a variety of pharmacological functions, specially targeting membrane proteins and interfering with the membrane permeability for Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup> and Cl<sup>-</sup> in excitable and non-excitable cells [1,2]. Scorpion venoms also contain enzymatic and cytolytic compounds. In general, scorpion venom compounds can be classified in two groups: disulfide-bridged peptides (DBP) that represent neurotoxins [3] and non-disulfide-bridged peptides (NDBP) [4]. Interestingly, scorpine, a compound isolated from *Pandinus imperator* venom [5], contains a region belonging to the DBP and another belonging to the NDBP. Scorpine was shown to display antibacterial and anti-parasitic activities, but also to modify normal function of potassium ion channels. Scorpine-like peptides have been discovered in other species of scorpions, for example in *Hadrurus gertschi* [6,7], *Tityus costatus* [8], *Opisthacanthus cayaporum* [9], *Pandinus cavimanus* [10], *Euscorpions validus* [11], *Urodacus yaschenkoi* [12], *Opisthophthalmus carinatus* [13], *Heterometrus laoticus* [14] and *Vaejovis* species [15].

## Structural Properties and Bioactivity of Scorpine-Like Peptides

The scorpine-like peptides belong to the third group of β-K<sup>+</sup> channel specific toxins (β-KTx) and were first called 'orphan peptides' because they showed contrasting pharmacological activity due to their bi-functionality [6,13,16]. The N-terminal region of scorpine-like peptides have cytolytic or antimicrobial activity like the insect cecropins (20% identity) with an alpha-helical structure that moves freely [16,17], while the C-terminal region has K<sup>+</sup> channel blocking activity and it is tightly folded by three disulfide bridges exhibiting a "cysteine stabilized α/β motif" (CS-α/β) [18]. The C-terminal domain is characterized by a conserved sequence: (x)<sub>3</sub>Cx(A)<sub>5</sub>GxCxHC(x)<sub>3</sub>ExKxGxCHGKCKC GxPLSY(x)<sub>1-4</sub>, obviously containing 3 disulfide bridges and following completely the typical Cys pattern of invertebrate defensins discussed by Froy and Gurevitz [17] (Figure 1). This segment is responsible for the activity on potassium channels (Table 1). The biological activity of some of these peptides have been investigated (Table 1).

## Antimicrobial and antiviral activity

Other examples of antimicrobial effect were reported. For instance, Opiscorpine showed anti-fungal activity against *Fusarium oxysporum*, a pathogen causing Fusarium wilt in many plants [13]. HgeScplp1 shows cytolytic activity at 200 nM in oocytes and erythrocytes and also inhibit the growth of *B. subtilis* at 2 μM [16]. In contrast, the recombinant



**Figure 1: Multiple sequence alignment and phylogenetic analysis. A).** All known scorpine-like peptides were aligned with GENEIOUS. Conserved residues on all sequences are in red and conservative replacements are in blue. The N-terminal domain includes residues from 1-43 whereas the residues 44-87 belong to the C-Caβ domain. Table 1 shows the accession numbers of each sequence to exception of peptides ViScplp1, ViScplp2 and ViScplp3 isolated from *Vaejovis intrepidus*; VpScplp1 from *Vaejovis punctatus*; VmScplp1, VmScplp2 and VmScplp3 from *Vaejovis mexicanus*; VsScplp1 from *Vaejovis subcristatus*, which were reported in Quintero-Hernández (2015). The percentage of identity was determined with LALIGN v.36.3.5 and the E-value with PSI-BLAST. **B).** The phylogenetic tree of scorpine-like peptides was constructed with the Neighbor-joining algorithm using GENEIOUS Software. Tree shows 22 scorpines grouped in three main clades. First clade similar to Heteroscorpine-1 grouping all the Opiscorpines, Panscorpine and Panscorpine. Second clade consists of scorpines similar to Hge-scorpine-1, short-chain-scorpine, having a few *Vaejovis* scorpine-like-peptides and one from *Urodacus*. The last clade contains large-chain-scorpines similar to Hge-scorpine-2 grouping the remaining *Vaejovis* scorpine-like peptides and the long scorpine from *Urodacus*.

version of the scorpine-like Ev37 did not show any antimicrobial or hemolytic activity at 20 and 10 μM concentrations [11]. It remains to

**\*Corresponding author:** Lourival D Possani, Departamento de Medicina Molecular y Bioprocesos, Instituto de Biotecnología, Universidad Nacional Autónoma de México, Avenida Universidad, 2001, Colonia Chamilpa, Apartado Postal 510-3, Cuernavaca 62210, México, Tel: +52-77-73121709; Fax: +52-77-73172388; E-mail: [possani@ibt.unam.mx](mailto:possani@ibt.unam.mx)

**Received** April 05, 2016; **Accepted** May 07, 2016; **Published** May 09, 2016

**Citation:** Luna-Ramírez K, Jiménez-Vargas JM, Possani LD (2016) Scorpine-Like Peptides. Single Cell Biol 5: 138. doi:10.4172/2168-9431.1000138

**Copyright:** © 2016 Luna-Ramírez K, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Scorpion species	Name	Length (aa)	Biological effects	Reference**
<i>Pandinus imperator</i>	Panscorpine	75	Active against bacteria ( <i>B. subtilis</i> and <i>K. pneumoniae</i> )	P56972, [5]
<i>Heterometrus laoticus</i>	Heteroscorpine-1	76	Active against <i>B.subtilis</i> , <i>K.pneumoniae</i> and <i>P.aeruginosa</i> .	P0C2F4, [14]
<i>Opisthophthalmus carinatus</i>	Opiscorpine-1	76	The short synthetic peptide (20-54aa) has antifungal activity against <i>F. culmorum</i> (IC <sub>50</sub> = 8.8 μM), <i>F. oxysporum</i> (IC <sub>50</sub> = 10 μM) and bacteria <i>P. aeruginosa</i> , <i>E. coli</i> .	Q5WR03, [13]
	Opiscorpine-2	76	Active against fungi and bacteria*	Q5WR01
	Opiscorpine-3	76	Active against fungi and bacteria*	Q5WQZ7
	Opiscorpine-4	76	Active against fungi and bacteria*	Q5WQZ9
<i>Pandinus cavimanus</i>	Pcascorpine1	73	Active against fungi and bacteria*	H2CYP8, [10]
<i>Opisthacanthus cayaporum</i>	OcyC7_fragment	53	Active against fungi and bacteria*	C5J891, [9]
<i>Hadrurus gertschi</i>	HgeScplp1	76	HgeScplp1 has antibacterial activity against <i>B.subtilis</i> . Also it has hemolytic and cytolytic activities on oocytes and erythrocytes. The short peptide (29-76aa) blocks Kv1.1 (IC <sub>50</sub> =185 nM) potassium channels. Shows a weak hemolytic activity	Q0GY40, [6,7]
	HgeScplp2	84	Active against fungi and bacteria*	P0C8W5, [7],
<i>Urodacus yaschenkoi</i>	Uroya_1	76	Active against fungi and bacteria*	L0G8Z0, [12]
	Uroya_2	83	Active against fungi and bacteria*	
<i>Vaejovis intrepidus</i>	ViScplp1	78	Active against fungi and bacteria*	[15]
	ViScplp2	78	Active against fungi and bacteria*	
	ViScplp3	85	Active against fungi and bacteria*	
<i>Vaejovis punctatus</i>	VpScplp1	78	Active against fungi and bacteria*	
<i>Euscorplops validus</i>	Ev37	78	Selectively inhibits Kv1.3 channel (IC <sub>50</sub> =0.95 μM).	P0DL47, [11]
<i>Vaejovis mexicanus</i>	VmScplp1	77	Active against fungi and bacteria*	[15]
	VmScplp2	84	Active against fungi and bacteria*	
	VmScplp3	85	Active against fungi and bacteria*	
<i>Vaejovis subscristatus</i>	VsScplp1	59	Active against fungi and bacteria*	
<i>Tityus costatus</i>	Tco41.46-2	68	Active against bacteria and may block Kv channels*	Q5G8A6, [8]

\*By similarity to other sequences may have the same activity;  
\*\*Sequence references are databank accession numbers (either SwissProt, TrEMBL or GenBank) as retrieved from www.ncbi.nih.gov/entrez (PDB codes, where available, are between parenthesis) or literature references.

Table 1: List of scorpine-like peptides obtained from the venom of various scorpions.

be shown whether the folding of the recombinant peptide is the correct one, necessary for activity. Scorpine was also demonstrated to affect viral replication in cell culture containing Dengue virus [19].

Antimalarial activity

Scorpine-like peptides have been used to control malaria, in special Scorpine, which has been recombinantly expressed in *Anopheles gambiae* cells showing antibacterial activity against *B. subtilis* and *K. pneumonia*, at 5 and 10 μM, respectively. It also produced 98% mortality in sexual stages of *Plasmodium berghei* (ookinetes) at 15 μM and 100% reduction in *P. falciparum* parasitemia at 5 μM [19]. Moreover, the overexpression and secretion of Scorpine into the hemolymph from transgenic mosquitoes reduced sporozoite counts by 98% just a few days after a *Plasmodium*-infected blood meal, suggesting that it could be a powerful weapon for combating malaria [19,20]. Interesting results were obtained by heterologous expression of Scorpine in a strain of *Metarhizium anisopliae* fungus that can parasite mosquitoes. A fusion protein made with a repeat of peptides [SM1]<sub>8</sub> with Scorpine directs the product to the salivary glands of the mosquitoes [20]. Infection with these transgenic fungi reduces 98% of *Plasmodium* sporozoites in the salivary gland. The expression of those genes shortened the time taken to reduce transmission of malaria compared to wild type *M. anisopliae* and can reduce transmission rates even when the mosquito has an advanced infection. *M. anisopliae* can infect *A. gambiae*, *A. arabiensis*, *A. funestus* and other populations of mosquitoes. This transgenic strategy could have a wider impact. It could potentially be used to tackle other diseases spread by mosquitoes and other insects [20].

Modulation of activity of potassium channels

The C-terminal region of HgeScplp1 blocks Kv1.1 channel currents (IC<sub>50</sub> 88 nM) [16] while the recombinant version Ev37 is able of inhibit the Kv1.3 channel current showing an IC<sub>50</sub> value of 1 μM [11].

Mechanism of Action

The mechanism of action of scorpine-like peptides on microbes probably is similar to that described for the scorpine-AMPs. The latest are generally defined by containing 2-9 positively charged lysine or arginine residues plus hydrophobic amino acids. These residues confer physicochemical properties permitting interactions with microbial membranes and enabling their typically broad-spectrum antimicrobial activity by directly disrupting the membrane [21]. The membrane is disrupted in several stages; first the electrostatic interaction of AMPs with the polyanionic surface of lipopolysaccharide on the bacterial membrane causes an increase in surface area that weakens the bilayer. This alteration leads to pore formation causing the cell lyses. The disruption can be explained by diverse models (barrel stave, carpet model or torodial model) but merely forming a pore that creates an aqueous channel in the microbe membrane that leads to the loss of polarization, loss of intracellular cellular contents, disturbance of membrane function from lipid redistribution and finally death [21,22].

In the antimalarial activity both domains may be involved, the cytolytic activity of the N-terminal and the blocking effect of the C-terminal on potassium channels, although there are few studies on the subject but the mechanism of action has not been elucidated [20,23].

## Concluding Remarks

Scorpine-like peptides are interesting compounds of scorpion venom that might aid against the fight towards multi-resistant drug bacteria, contribute to the understanding of potassium ion channels, control viral replication and help in combating malaria. The N-terminal region of scorpine-like peptides might provide antimicrobial and antifungal activities, whereas the C-terminal region might provide novel potassium channel modulators. The critical aspect would be to cleave the peptide in such a way to create (1) a potent AMP with the linear region of scorpine-like peptides and on the other hand, (2) a specific ion channel modulator that contains the motifs that provide the bioactivity.

Scorpines have shown promising antimalarial activity. By producing transgenic mosquitoes that express recombinant scorpines, the malaria parasite transmission can be interrupted. This effect is due to the bi-functionality of scorpine-like peptides. However, our understanding of the mechanism of action of scorpine-like peptides towards parasites and viruses remains unclear. All these evidences make scorpine-like peptides attractive compounds for further research and development into drug leads.

## Acknowledgements

Partially supported by grants from SEP-CONACyT No. 237864 and DGAPA-UNAM IN203416 to LDP.

## References

- Possani LD, Becerril B, Delepierre M, Tytgat J (1999) Scorpion toxins specific for Na<sup>+</sup>-channels. *Eur J Biochem* 264: 287-300.
- Rodríguez de la Vega RC, Merino E, Becerril B, Possani LD (2003) Novel interactions between K<sup>+</sup> channels and scorpion toxins. *Trends Pharmacol Sci* 24: 222-227.
- Rodríguez de la Vega RC, Possani LD (2004) Current views on scorpion toxins specific for K<sup>+</sup>-channels. *Toxicon* 43: 865-875.
- Zeng XC, Corzo G, Hahin R (2005) Scorpion venom peptides with no disulfide bridge. *IUBMB Life* 57: 13-21.
- Conde R, Zamudio FZ, Rodríguez MH, Possani LD (2000) Scorpine, an anti-malaria and anti-bacterial agent purified from scorpion venom. *FEBS Lett* 471: 165-168.
- Diego-García E, Schwartz EF, D'Suze G, González SA, Batista CV, et al. (2007) Wide phylogenetic distribution of Scorpine and long-chain  $\beta$ -KTx-like peptides in scorpion venoms: identification of "orphan" components. *Peptides* 28: 31-37.
- Schwartz EF, Diego-García E, Rodríguez de la Vega RC, Possani LD (2007) Transcriptome analysis of the venom gland of the Mexican scorpion *Hadrurus gertschi* (Arachnida: Scorpiones). *BMC Genomics* 8: 119.
- Diego-García E, Batista CV, García-Gómez BI, Lucas S, Candido DM, et al. (2005) The Brazilian scorpion *Tityus costatus* Karsch: genes, peptides and function. *Toxicon* 45: 273-283.
- Silva EC, Camargos TS, Maranhão AQ, Silva-Pereira I, Silva LP, et al. (2009) Cloning and characterization of cDNA sequences encoding for new venom peptides of the Brazilian scorpion *Opisthacanthus cayaporum*. *Toxicon* 54: 252-261.
- Diego-García E, Peigneur S, Clynen E, Marien T, Czech L, et al. (2012) Molecular diversity of the telson and venom components from *Pandinus cavimanus* (Scorpionidae Latreille 1802): Transcriptome, Venomics and Functions. *Proteomics* 12: 313-328.
- Feng J, Yu C, Wang M, Li Z, Wu Y, et al. (2013) Expression and characterization of a novel scorpine-like peptide Ev37, from the scorpion *Euscorplops validus*. *Protein Expr Purif* 88: 127-133.
- Luna-Ramírez K, Quintero-Hernández V, Vargas-Jaimes L, Batista CV, Winkel KD, et al. (2013) Characterization of the venom from the Australian scorpion *Urodacus yaschenko*: Molecular mass analysis of components, cDNA sequences and peptides with antimicrobial activity. *Toxicon* 63: 44-54.
- Zhu S, Tytgat J (2004) The scorpine family of defensins: gene structure, alternative polyadenylation and fold recognition. *Cell Mol Life Sci* 61: 1751-1763.
- Uawonggul N, Thammasirak S, Chaveerach A, Arkaravichien T, Bunyatratchata W, et al. (2007) Purification and characterization of Heteroscorpine-1 (HS-1) toxin from *Heterometrus laoticus* scorpion venom. *Toxicon* 49: 19-29.
- Quintero-Hernández V, Ramírez-Carreto S, Romero-Gutiérrez MT, Valdez-Velázquez LL, Becerril B, Possani LD, et al. (2015) Transcriptome Analysis of Scorpion Species Belonging to the *Vaejovis* Genus. *PLoS One* : 1-18.
- Diego-García E, Abdel-Mottaleb Y, Schwartz EF, de la Vega RC, Tytgat J, et al. (2008) Cytolytic and K<sup>+</sup> channel blocking activities of beta-KTx and scorpine-like peptides purified from scorpion venoms. *Cell Mol Life Sci* 65: 187-200.
- Froy O, Gurevitz M (2003) New insight on scorpion divergence inferred from comparative analysis of toxin structure, pharmacology and distribution. *Toxicon* 42: 549-555.
- Mouhat S, Jouirou B, Mosbah A, De Waard M, Sabatier JM (2004) Diversity of folds in animal toxins acting on ion channels. *Biochem J* 378: 717-726.
- Carballar-Lejarazú R, Rodríguez MH, de la Cruz Hernández-Hernández F, Ramos-Castañeda J, Possani LD, et al. (2008) Recombinant scorpine: a multifunctional antimicrobial peptide with activity against different pathogens. *Cell Mol Life Sci* 65: 3081-3092.
- Fang W, Vega-Rodríguez J, Ghosh A, Jacobs-Lorena M, Kang A, et al. (2011) Development of Transgenic Fungi That Kill Human Malaria Parasites in Mosquitoes. *Science* 331: 1074-1077.
- Jenssen H, Hamill P, Hancock RE (2006) Peptide antimicrobial agents. *Clin Microbiol Rev* 19: 491-511.
- Harrison PL, Abdel-Rahman MA, Miller K, Strong PN (2014) Antimicrobial peptides from scorpion venoms. *Toxicon* 88: 115-137.
- Zhu S, Gao B, Amelas A, Rodríguez MC, Lanz-Mendoza H, et al. (2010) MeuTXKB, a scorpion venom-derived two-domain potassium channel toxin-like peptide with cytolytic activity. *Biochimica et Biophysica Acta* 1804: 872-883.

## OMICS International: Publication Benefits & Features

### Unique features:

- Increased global visibility of articles through worldwide distribution and indexing
- Showcasing recent research output in a timely and updated manner
- Special issues on the current trends of scientific research

### Special features:

- 700 Open Access Journals
- 50,000 editorial team
- Indexing at major indexing services
- Rapid review process
- Quality and quick editorial, review and publication processing
- Indexing at PubMed (partial), Scopus, DOAJ, EBSCO, Index Copernicus and Google Scholar etc
- Sharing Option: Social Networking Enabled
- Authors, Reviewers and Editors rewarded with online Scientific Credits
- Better discount for your subsequent articles

Submit your manuscript at: <http://www.omicsonline.org/submission/>

Citation: Luna-Ramírez K, Jiménez-Vargas JM, Possani LD (2016) Scorpine-Like Peptides. Single Cell Biol 5: 138. doi:[10.4172/2168-9431.1000138](https://doi.org/10.4172/2168-9431.1000138)