



# New aspects in snake venom toxicology

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Snakebite envenomation causes > 81,000 deaths and incapacities in another 400,000 people worldwide every year. Snake venoms are complex natural secretions comprised of hundreds of different molecules with a wide range of biological functions, which after injection cause local and systemic toxic manifestations (Di Nicola 2021; Acunha et al 2021).

Against this background, snake venom toxicology is a field of high toxicological impact that has attracted increased interest over the last decade. This is reflected by publications in Archives of Toxicology. Traditionally, toxicologists were primarily interested in snake venom effects on blood coagulation (Klöcking and Hoffmann 1991; Wiwanitkit 2006; Sanchez et al. 2009), a relevant field that continues as an important research matter (Teixeira et al 2011, Giron et al. 2013; Zheng et al. 2013, Sartim et al 2016). Other aspects are cytotoxicity (El Hakim 2011), neurotoxicity (Floriano et al 2019), and immunological effects (Silva da Franca et al. 2021) of snake venom constituents.

The scientific focus of recent articles has broadened, as clinical (Abd El-Aziz et al 2020) and pharmacological matters (Lee et al 2016) were incorporated. The latter aspect is highlighted in current reviews as a cutting-edge topic (Bordon et al 2020; Kalita et al 2021; Akhtar et al 2021). Here, the potential of snake venom constituents for cancer treatment is particularly promising. In this context, progress into identification of constituents of snake venom proteomes is important (Estrella et al 2011; Igci and Demiralp 2012).

The majority of studies have focused on the protein portion (toxins), without paying significant attention to other fractions. A heretofore neglected field is that of lipid constituents of snake venoms. A breakthrough in this new area was just reported in this journal. Acunha et al (2021) reported about an untargeted lipidomic approach, based on liquid chromatography with high-resolution mass spectrometry.

This was applied to investigate the lipid constituents of venoms of the South American snakes *Crotalus durissus terrificus* and *Bothrops moojeni*. Phosphatidylcholines (PC), Lyso-PCs, phosphatidylethanolamines (PE), Lyso-PE, phosphatidylserine, phosphatidylinositol, ceramides, and sphingomyelin species were detected. The lipids included bioactive compounds such as platelet-activating factor (PAF) precursor, PAF-like molecules, plasmalogens, ceramides, and sphingomyelins with long fatty acid chain lengths, which may be associated with the systemic responses triggered by *Crotalus durissus terrificus* and *Bothrops moojeni* envenomation. The responses include platelet aggregation, activation of intercellular adhesion molecule 1 (ICAM1), apoptosis, as well as the production of pro-inflammatory lipid mediators, cytokines, and reactive species. The new lipidomics aspects will contribute to an increased understanding of the complex pathology elicited by snakebite envenomation.

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## Declarations

**Conflict of interest** The author declared not to have actual or potential competing financial interests.

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## References

- Abd El-Aziz TM, Shoukamy MI, Hegazy AM, Stockand JD, Mahmoud A, Mashaly AMA (2020) Comparative study of the in vivo toxicity and pathophysiology of envenomation by three medically important Egyptian snake venoms. *Arch Toxicol* 94(1):335–344. <https://doi.org/10.1007/s00204-019-02619-y>
- Acunha T, Nardini V, Faccioli LH (2021) A lipidomics approach reveals new insights into *Crotalus durissus terrificus* and *Bothrops moojeni* snake venoms. *Arch Toxicol* 95(1):345–353. <https://doi.org/10.1007/s00204-020-02896-y>
- Akhtar B, Muhammad F, Sharif A, Anwar MI (2021) Mechanistic insights of snake venom disintegrins in cancer treatment. *Eur J Pharmacol* 899:174022. <https://doi.org/10.1016/j.epharm.2021.174022> (Online ahead of print)
- Bordon KCF, Cologna CT, Fornari-Baldo EC, Pinheiro-Júnior EL, Cerni FA, Amorim FG, Anjolette FAP, Cordeiro FA, Wiesel GA, Cardoso IA, Ferreira IG, de Oliveira IS, Boldrini-França J, Pucca MB, Baldo MA, Arantes EC (2020) From animal poisons and venoms to medicines: achievements, challenges and perspectives in drug discovery. *Front Pharmacol* 11:1132. <https://doi.org/10.3389/fphar.2020.01132.eCollection>
- Di Nicola MR, Pontara A, Kass GEN, Kramer NI, Avella I, Pampena R, Mercuri SR, Dorne JLCM, Paolino G (2021) Vipers of major clinical relevance in Europe: taxonomy, venom composition, toxicology and clinical management of human bites. *Toxicology* 453:152724. <https://doi.org/10.1016/j.tox.2021.152724>. Epub
- El Hakim AE, Gamal-Eldeen AM, Shahein YE, Mansour NM, Wahby AF, Abouelella AM (2011) Purification and characterization of a cytotoxic neurotoxin-like protein from *Naja haje haje* venom that induces mitochondrial apoptosis pathway. *Arch Toxicol* 85(8):941–952. <https://doi.org/10.1007/s00204-010-0631-8>
- Estrella A, Sánchez EE, Galán JA, Tao WA, Guerrero B, Navarrete LF, Rodríguez-Acosta A (2011) Characterization of toxins from the broad-banded water snake *Helicops angulatus* (Linnaeus, 1758): isolation of a cysteine-rich secretory protein, Helicopsin. *Arch Toxicol* 85(4):305–313. <https://doi.org/10.1007/s00204-010-0597-6>
- Floriano RS, Schezaro-Ramos R, Silva NJ Jr, Bucarety F, Rowan EG, Hyslop S (2019) Neurotoxicity of *Micrurus lemniscatus lemniscatus* (South American coral snake) venom in vertebrate neuromuscular preparations in vitro and neutralization by antivenom. *Arch Toxicol* 93(7):2065–2086. <https://doi.org/10.1007/s00204-019-02476-9>
- Girón ME, Rodríguez-Acosta A, Salazar AM, Sánchez EE, Galán J, Ibarra C, Guerrero B (2013) Isolation and characterization of two new non-hemorrhagic metalloproteinases with fibrinogenolytic activity from the mapanare (*Bothrops colubriensis*) venom. *Arch Toxicol* 87(1):197–208. <https://doi.org/10.1007/s00204-012-0914-3>
- Igci N, Demiralp DO (2012) A preliminary investigation into the venom proteome of *Macrovipera lebetina obtusa* (Dwigubsky, 1832) from Southeastern Anatolia by MALDI-TOF mass spectrometry and comparison of venom protein profiles with *Macrovipera lebetina lebetina* (Linnaeus, 1758) from Cyprus by 2D-PAGE. *Arch Toxicol* 86(3):441–451. <https://doi.org/10.1007/s00204-011-0763-5>
- Kalita B, Saviola AJ, Mukherjee AK (2021) From venom to drugs: a review and critical analysis of Indian snake venom toxins envisaged as anticancer drug prototypes. *Drug Discov Today*. <https://doi.org/10.1016/j.drudis.2020.12.21> (Online ahead of print)
- Klöcking HP, Hoffmann A (1991) Effects of snake venoms on tissue-type plasminogen activator release. *Arch Toxicol Suppl* 14:157–159. <https://doi.org/10.1007/978-3-642-74936-0-31>
- Lee HL, Park MH, Hong JE, Kim DH, Kim JY, Seo HO, Han SB, Yoon JH, Lee WH, Song HS, Lee JI, Lee US, Song MJ, Hong JT (2016) Inhibitory effect of snake venom toxin on NF- $\kappa$ B activity prevents human cervical cancer cell growth via increase of death receptor 3 and 5 expression. *Arch Toxicol* 90(2):463–477. <https://doi.org/10.1007/s00204-014-1393-5>
- Sánchez EE, Rodríguez-Acosta A, Palomar R, Lucena SE, Bashir S, Soto JG, Pérez JC (2009) Colombistatin: a disintegrin isolated from the venom of the South American snake (*Bothrops colombiensis*) that effectively inhibits platelet aggregation and SK-Mel-28 cell adhesion. *Arch Toxicol* 83(3):271–279. <https://doi.org/10.1007/s00204-008-0358-y>
- Sartim MA, Costa TR, Laure HJ, Espindola MS, Frantz FG, Sorgi CA, Cintra AC, Arantes EC, Faccioli LH, Rosa JC, Sampaio SV (2016) Moojenactivase, a novel pro-coagulant PIII metalloprotease isolated from *Bothrops moojeni* snake venom, activates coagulation factors II and X and induces tissue factor up-regulation in leukocytes. *Arch Toxicol* 90(5):1261–1278. <https://doi.org/10.1007/s00204-015-1533-6>
- Silva de França F, Gabrili JJM, Mathieu L, Burgher F, Blomet J, Tambourgi DV (2021) *Bothrops lanceolatus* snake (Fer-de-lance) venom triggers inflammatory mediators' storm in human blood. *Arch Toxicol* 95(3):1129–1138. <https://doi.org/10.1007/s00204-020-02959-0>
- Teixeira SS, Silveira LB, da Silva FM, Marchi-Salvador DP, Silva FP Jr, Izidoro LF, Fuly AL, Juliano MA, dos Santos CR, Murakami MT, Sampaio SV, da Silva SL, Soares AM (2011) Molecular characterization of an acidic phospholipase A(2) from *Bothrops pirajai* snake venom: synthetic C-terminal peptide identifies its antiplatelet region. *Arch Toxicol* 85(10):1219–1233. <https://doi.org/10.1007/s00204-011-0665-6>
- Wiwantit V (2006) Thrombin-like effect of an important green pit viper toxin, albolabrin: a bioinformatic study. *Arch Toxicol* 80(12):829–832. <https://doi.org/10.1007/s00204-006-0108-y>
- Zeng F, Shen B, Zhu Z, Zhang P, Ji Y, Niu L, Li X, Teng M (2013) Crystal structure and activating effect on RyRs of AhV\_TL-I, a glycosylated thrombin-like enzyme from *Agkistrodon halys* snake venom. *Arch Toxicol* 87(3):535–545. <https://doi.org/10.1007/s00204-012-0957-5>

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