v.1 n.2(2023): 4.
https://doi.org/10.29327/2256856.1.2-4
ISSN 2965-4084

https://faculdadececape.edu.br/revista-kariri-science/

Review

Antiproliferative activity of snake venom-derived phospholipase classes against tumor cell lines: A systematic review

Vanessa P. G. Ferreira [1,2], Gabriel A. de Moura[2,3], Yasmim M. Rocha,[2,3], João P. V. Rodrigues[2,3], Roberto Nicolete[1,2,3].

[1] Graduate Program in Biotechnology, Northeast Network in Biotechnology (RENORBIO), State University of Ceará (UECE), Fortaleza - Ceará, Brazil; renorbio.ce@uece.br
[2] Oswaldo Cruz Foundation (Fiocruz Ceará), Eusébio – Ceará, Brazil https://portal.fiocruz.br/
[3] Graduate Program in Pharmaceutical Sciences (PPGCF), Federal University of Ceará (UFC); Fortaleza - Ceará, Brazil. pgcf.ufc@gmail.com

***Correspondence:** vanessa.pinheiro@fiocruz.com.br; roberto.nicolete@fiocruz.com.br.

Abstract: Cancer is a global public health problem and one out of every six deaths in the world is caused by cancer. Among the different types of this pathology, melanoma-type skin cancer stands out. It is the most lethal of all in its metastatic state with characteristics of acquiring resistance to various therapies. Studies carried out with crotoxin extracted from the venom of *Crotalus durissus terrificus* have already confirmed in vitro cytotoxic activity against melanoma the present work aims to investigate, through a systematic review of the literature, the potential antitumor activity of phospholipase derived from snake venom against tumor cell lines in vitro studies; For this purpose, searches were performed in the Pubmed, Embase and Lilacs databases. The search was performed by combining the descriptors Phospholipase A2, Snake venoms and Antitumoral. The inclusion criteria: in vivo experimental articles and in vitro experimental articles. Exclusion criteria: articles that were out of scope, review articles, abstracts, and letters to the reader. Data extracted were: author; type of study; class of phospholipase or derivative; effective concentration used alone or in combination; cytotoxicity in vitro and/or in vivo; biological activity; and tumoral cell line tested. As addressed in the databases, the search found 44 articles; 15 were selected. In this review, it was identified that 28 cell lines tested. The tested molecules showed effectiveness at concentrations ranging from 9.25 - 350 μM. As main biological activities, PLA2s showed an increase in apoptosis rate in tumor cell lines In the studies, a reduction in the adhesion rate of tumor cell lines was also In addition, an increase in the rate of cell apoptosis was observed. Delayed cell cycle progression of tumor cell lines e and tumor volume in vivo. In addition, this review identified that the molecules could cause cytotoxic activity in non-tumor lineages at concentrations of 37 μM and 350 mM. In conclusion, this work demonstrates the importance of PLA2, indicating its potential use as a tool to identify pharmacological targets and as a prototype for developing new anticancer therapies.

Keywords: Phospholipase A2, Snake venoms and Antitumor.

Citation: Ferreira *et al.*, Antiproliferative activity of snake venom-derived phospho-lipase classes against tumor cell lines: A systematic review

Kariri Science – CECAPE Biology and Health Journal v.1 n.2(2023): 4. https://doi.org/10.29327/2256856.1.2-4

Associate Editor: Henrique D. M. Coutinho

Received: 27 April 2023
Accepted: 28 July 2023
Published: 26 December 2023

1. Introduction

The introduction should briefly place the study in a broad context and highlight why it is important. It should define the purpose of the work and its significance. The current state of the research field should be carefully reviewed and key publications cited. Please highlight controversial and diverging hypotheses when necessary. Finally, briefly mention the main aim of the work and highlight the principal conclusions. As far as possible, please keep the introduction comprehensible to scientists outside your particular field of research. References should be numbered in order of appearance and indicated by a

numeral or numerals in square brackets—e.g., [1] or [2,3], or [4–6]. See the end of the document for further details on references. Cancer (CA) is characterized as a heterogeneous syndrome that can manifest from different pathways, leading to mutations in the activity of oncogenes and tumor suppressor genes [24]. As a result of this dysregulation, abnormal cell growth with differentiated phenotypes will potentially proliferate into adjacent cells or organs, thus predicting tumor malignancy [33]. According to data from the World Health Organization (WHO), cancer is the leading cause of death worldwide, corresponding to about 9.6 million deaths in 2018 [34]. It is worth noting that for most patients presenting with advanced solid tumors, treatment is not administered with curative intent but in hopes of improving survival and/or symptom relief [17].

Currently, it is known that there is a series of patterns that define tumors, these being called the hallmarks of cancer that are taken as the increase and sustainment of proliferative activity, evasion of growth suppressors, resistance to death, enabling replicative immortality that induces angiogenesis, activate invasion and metastasis collaborating to disease progression [14]. Moreover, another factor that has generated significant concern worldwide is the phenomenon of multiple drug resistance (MDR) in cancer, which is characterized as the refractoriness of target cells to a chemotherapeutic drug accompanied by resistance to other drugs with different mechanisms of action and structure [26]. In this context, there is a growing effort to identify new biologically active molecules that can treat these tumors [7].

Snake venoms comprise a vast biological library of toxins that can be used for various applications [28]. Among these molecules is crotoxin (CTX) which is characterized as a heterodimeric β-neurotoxin formed by the non-covalent association between two subunits, one of them the Crotoxin A or crotapotin acid and a base called crotoxin B or phospholipase A2 (PLA2) [19]. PLA2s consist of three α-helices, a highly conserved protein, the calcium-binding loop, two antiparallel β-strains, and a catalytically inactive flexible C-terminal loop. Their toxic effects are still unknown. However, they still possess more significant toxicity than their catalytically active counterparts [29] to which PLA2s are among the most studied and well-characterized snake venom toxins due to their catalytic role that exhibits multiple biological activities of pharmaceutical interest [18].

In a previous study, Côrrea et al.[9] (2016) found that the PLA2-derived peptide BnuTX-I demonstrated antimicrobial activity at concentrations ranging from 50-100 μg/mL against Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, and Staphylococcus aureus strains. SALES et al., 2017 verified a potential anti-inflammatory activity from the molecular docking of two PLA2 molecules derived from snake venom, showing the pharmaceutical potential against different pathologies. Therefore, the present work aims to investigate, through a systematic review of the literature, the potential antitumor activity of phospholipase derived from snake venom against tumor cell lines in vitro studies.

2. Materials and Methods

The Materials and Methods should be described with sufficient details to allow others to replicate and build on the published results. Please note that the publication of your manuscript implicates that you must make all materials, data, computer code, and protocols associated with the publication available to readers. Please disclose at the submission stage any restrictions on the availability of materials or information. New methods and protocols should be described in detail while well-established methods can be briefly described and appropriately cited.

Research manuscripts reporting large datasets that are deposited in a publicly available database should specify where the data have been deposited and provide the relevant accession numbers. If the accession numbers have not yet been obtained at the time of submission, please state that they will be provided during review. They must be provided prior to publication.

Interventionary studies involving animals or humans, and other studies that require ethical approval, must list the authority that provided approval and the corresponding ethical approval code.

3. Results and Discussion

As addressed in the databases, the search found 44 articles; 15 were selected. The collection and screening protocol is described in Figure 1. In this review, it was identified that 28 cell lines tested (B16, EMT6, S-180, P3X, HT1080, IGR39, HT29-D4, B16F10, SKBR3, S49, A549, MDA-MB-231, KYSE 30, KYSE 270, GAMG, HCB151, U373, PSN-1, PANC-1, HeLa, SiHa, MCF7, MCF10A, CCL-107, HTB-186, Caco-2, RD, NCI-H292). Among the studies reviewed, only three PLA2s were chemically synthesized (Lys49 PLA2, BthTX-I, AP-1). The others were extracted from snake venom (MVL-PLA2, PLA 2, [Ser 49] PLA 2, BnSP-6 PLA2, MjTX-I, F1 CTX, PLA2 BthTX-II, Crotoxin, and BmPLA2). All data is presented in Table 1.

The tested molecules showed effectiveness at concentrations ranging from 9.25 - 350 μM. As main biological activities, PLA2s showed an increase in apoptosis rate in tumor cell lines [2,3,6,16,21,26]. In the studies, a reduction in the adhesion rate of tumor cell lines was also observed [2,3,4,5,19]. In addition, an increase in the rate of cell apoptosis was observed [2]. Delayed cell cycle progression of tumor cell lines [3,16] e and tumor volume in vivo [21]. In addition, this review identified that the molecules could cause cytotoxic activity in non-tumor lineages at concentrations of 37 μM and 350 mM.

Snake venoms are recognized for their biochemical complexity, composed of a mixture of proteins, enzymes, peptides, and inorganic compounds, which may present different biological activities [31]. These bioactive compounds found in venom toxins represent a little-explored reservoir that can be directed to discover other molecular mechanisms activated by the venom besides targeting a wide variety of pharmacological targets for the treatment of several diseases [32].

With this in mind, we decided to study the effects of snake venom-derived phospholipase on tumor cell lines in vitro. Overall, our analysis suggests that phospholipase A2 (PLA2) showed apoptotic activity in most assays presented in this review, with retardation of cell cycle progression and tumor volume in vivo. Some studies have provided evidence that snake venom toxins, particularly PLA2, have the potential for the development of antitumor drugs [1,36].

Some studies showed increased apoptosis cell rate, as demonstrated by Lee et al.[21], (2015), Azevedo et al.[2] (2016), Muller et al.[26] (2018) and Azevedo et al.[3] (2019). For example, Lee et al.[21] (2015) demonstrated that the toxin inhibited the growth of lung cancer cells (A549 and NCl-H460) through inhibition of peroxiredoxin 6 (PRDX6), as PRDX6 attenuates apoptosis in human ovarian cancer cells via interaction with activator protein-1 (AP-1). Another study corroborates with the previous finding, which demonstrated that transgenic mice with PRDX6 overexpression were associated with an increase in AP-1 activity and, consequently, with increased lung tumor rate [23].

As well as Azevedo et al.[2] (2016) and Azevedo et al.[3] (2019), in this review, it was decided to investigate the antitumor effect of PLA2 isolated from Bothrops pauloensis and Bothrops jararacussu on human breast cancer MDA-MB-231 cells, and perceived, by cell death analysis, stimulation in the autophagy process, evidenced by the marking of parasitophorous vacuoles and autophagy process, respectively. Interestingly, PLA2 showed a possible target preference in cancer cells through cytotoxicity compared to non-cancerous breast cells. It corroborates with the study by Yan et al., 2007, in which the author demonstrated that both autophagy and apoptosis were activated in killing breast cancer cells by crotoxin, a cytotoxic PLA2.

The occurrence of apoptosis was also confirmed in the studies by Bennati et al.[6] (2018) and Jimenez-Charris et al.[16] (2019), through activation of the intrinsic and extrinsic pathway, by K562-S and K562-R cells, upon activation of caspases 3,8 and 9 and stimulated cell death by apoptosis in HeLa cervical carcinoma cells, suggesting a possible trigger

through extrinsic pathways, such as caspase 8. In line with previous findings, a cardiotoxin isolated from the snake's venom attracted also inhibited apoptosis in MCF-7 human cancer cells, confirmed by externalization of phosphatidylserine and cleavage of poly (ADP-ribose) polymerase [16].

Another study in this review was described by Bazaa et al.[5] (2009) and Azevedo et al.[3] (2019), who evaluated and characterized the impact of integrin inhibition using an MVL-PLA2 and BthTX-II on the behavior of vascular endothelial cells and breast cancer cells. It was demonstrated that these phospholipases inhibited the adhesion and migration of these cells, in addition to the elimination of angiogenesis both *in vitro* and *in vivo*, leading to changes in adhesion formation and specific inhibition of integrins $\alpha 5\beta 1$, $\alpha v\beta 3$, and $\alpha v\beta 6$. Notably, as seen in previous experiments, BthTX-II (PLA2-Asp49) was able to inhibit cell adhesion on both collagen and fibronectin, corroborating with the finding that integrin expression levels ($\beta 1$ and $\alpha 2$) decreased with treatment [13].

Our review showed that in two studies, there was cell cycle arrest in tumor cells of breast cancer strains [3,16]. There is a hypothesis that infers that PLA2 has a synergistic effect at the level of cell proliferation from the phosphorylation of serines or accumulation of phosphatidylcholine that eventually reflects in some activities, depending on its location, to which interference in this flow will lead to a modulation in the coordination of the proliferative response to intra and extracellular stimuli [15].

These findings can be confirmed in previous work by Manguikian, Barbour[22] (2004), who using Jurkat T cells, verified that the expression levels of phosphatidylcholine are modulated according to the phase of the cell cycle. Consequently, PLA2 showed its direct action on the cell cycle.

In this sense, it was described, through a systematic review of the literature, the main mechanisms involved by the different PLA2, which, according to this study, were able to inhibit tumor growth and metastasis, such as adhesion, migration, invasion, and changes in the cell cycle. Thus, this work demonstrates the importance of PLA2, indicating its potential use as a tool to identify pharmacological targets and as a prototype for developing new anticancer therapies.

3.2. Figure 1 and Table 1

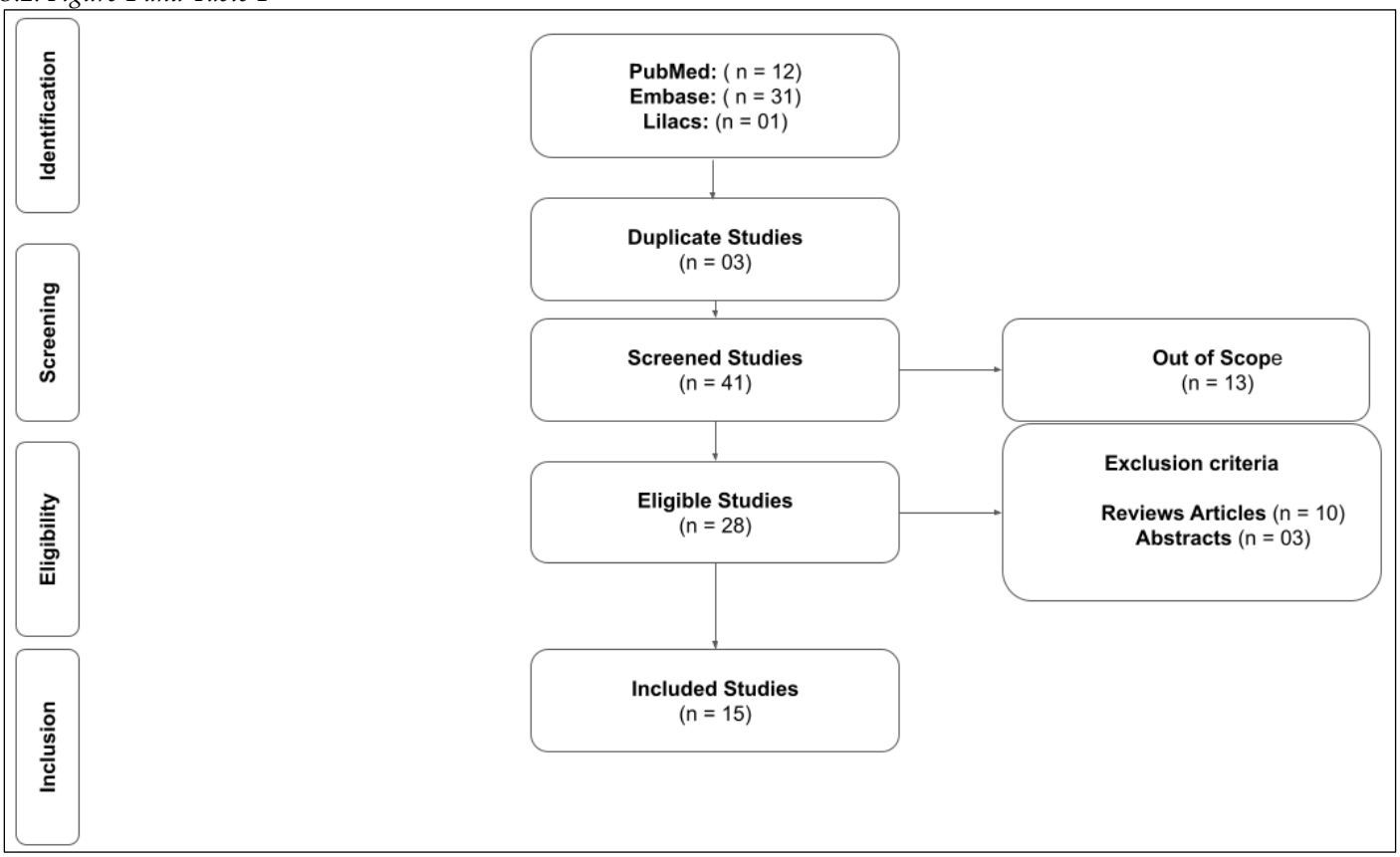

Figure 1. Methodological Screening

Table 1. Antitumor activity of phospholipases derived from snake venom.

Author	Cell Line	Source	Snake Specie	Phospholipase Type	Effective Concentration	Cytotoxicity	Effect
ARAYA & LOMONTE, 2007	B16; EMT6; S-180; P3X	Synthetic	*Agkistrodon piscivorus, Bothrops asper*	Lys49 PLA2	50-350 mM	50-350 mM	—
BAZAA *et al.*, 2009	HT1080; IGR39; HT29-D4	Natural	*Macrovipera lebetina trasmediterranea*	MVL-PLA2	35 - 100 nM	—	↓ Cell adhesion ↓ Cell migration
GEBRIM *et al.*, 2009	B16F10; SKBR3;	Synthetic	—	BthTX-I	1 µg/mL	—	—
NELSON *et al.*, 2013	S49	Natural	*Agkistrodon piscivorus piscivorus*	PLA 2	200 nM	—	—

CONLON *et al.*, 2013	A549	Natural	*Echis coloratus; Piramidum leakeyi; Echis carinatus sochureki*	[Ser 49]PLA 2	2.9-8.5 μM	> 100 μM	—
LEE *et al.*, 2015	A549	Synthetic	*Vipera lebetina turanica*	AP-1	6,8 μg/mL	—	↑ Apoptosis ↓ *In vivo* tumor volume
AZEVEDO *et al.*, 2016	MDA-MB-231	Natural	*Bothrops pauloensis*	BnSP-6 PLA2	12,5-100 μg/mL	—	↑ Autophagy ↑ Apoptosis ↓ Cell adhesion
BENNATI *et al.*, 2018	K562	Natural	*Bothrops moojeni*	MjTX-I	191-275 μg/mL	300 - 400 μg/mL	↑ Apoptosis
MULLER *et al.*, 2018	KYSE 30, KYSE 270, GAMG, HCB151, U373, PSN-1, PANC-1, HeLa, SiHa	Natural	*Crotalus durissus terrificus*	F1 CTX	0.5 - >30 ug/mL	No toxicity	↑ Apoptosis
JIMENEZ-CHARRIS *et al.*, 2019	MDA–MB–231; MCF7	Natural	*Porthidium lansbergii lansbergii*	Asp49-PLA 2	0,8-100 μg/mL	No toxicity	↑ Apoptosis ↓ Cell cycle
AZEVEDO *et al.*, 2019	MCF10A; MDA-MB-231	Natural	*Bothrops jararacussu*	PLA2 BthTX-II	10 - 50 ug/mL (MDA-MB-231)	No toxicity	↑ Apoptosis ↓ Cell cycle ↓ Cell adhesion

KATO & SAMPAIO, 2021	A549	Natural	*Crotalus durissus terrificus*	Crotoxin	12, 5 nM	No toxicity	↓ Cell adhesion
AZEVEDO *et al.*, 2022	MDA-MB-231	Natural	*Bothrops jararacussu*	Asp-49 PLA 2 BthTx-II	10 μg/mL	12,50 - 50 μg/mL	↓ Cell adhesion
LAZCANO-PÉREZ *et al.*, 2022	CCL-107; HTB-186	Natural	*Crotalus molossus nigrescens*	PLA2 BthTX-II	10 - 100 ng/mL	—	—
FRIHLING *et al.*, 2022	Caco-2; RD; NCI-H292	Natural	*Bothrops moojeni*	BmPLA2	9,25 uM (Caco-2, RD)	37 μM	—

References

1. ARAYA, C.; LOMONTE, B. Antitumor effects of cationic synthetic peptides derived from Lys49 phospholipase A2 homologues of snake venoms. Cell Biology International, v. 31, n. 3, p. 263-268, 2007.
2. AZEVEDO, F.; LOPES, D.; GIMENES, S.; ACHÊ, C.; VECCHI, L.; ALVES, P.; GUIMARÃES, D.; RODRIGUES, R.; RODRIGUES, L.; GERALDO, K. Human breast cancer cell death induced by BnSP-6, a Lys-49 PLA2 homologue from Bothrops pauloensis venom. International Journal of Biological Macromolecules, v. 82, p. 671-677, 2016.
3. AZEVEDO, F.; ZÓIA, M.; LOPES, D.; GIMENES, S.; VECCHI, L.; ALVES, P.; RODRIGUES, R.; SILVA, A.YONEYAMA, K.; GOULART, L.; RODRIGUES, V. Antitumor and antimetastatic effects of PLA2-BthTX-II from Bothrops jararacussu venom on human breast cancer cells. International Journal of Biological Macromolecules, v. 135, p. 261-273, 2019.
4. AZEVEDO, F.; LOPES, D.; ZÓIA, M.; CORREIA, L.; SAITO, N.; FONSECA, B.; POLLONI, L.; TEIXEIRA, S.; GOULART, L.; ÁVILA, V. A New Approach to Inhibiting Triple-Negative Breast Cancer: In Vitro, Ex Vivo and In Vivo Antiangiogenic Effect of BthTx-II, a PLA2-Asp-49 from Bothrops jararacussu Venom. Biomolecules, v. 12, n. 2, p. 258, 2022.
5. BAZAA, A.; LUIS, J.; SRAIRI-ABID, N.; KALLECHI-ZIRI, O.; KESSENTINI-ZOUARI, R.; DEFFILES, C.; LISSITZKY, J.; AYEB, M.; MARRAKCHI, M. MVL-PLA2, a phospholipase A2 from Macrovipera lebetina transmediterranea venom, inhibits tumor cells adhesion and migration. Matrix Biology, v. 28, n. 4, p. 188-193, 2009.
6. BENATTI, R.; COSTA, T.; CACEMIRO, M.; SAMPAIO, S.; CASTRO, F.; BURIN, S. Cytotoxic and pro-apoptotic action of MjTX-I, a phospholipase A2 isolated from Bothrops moojeni snake venom, towards leukemic cells. Journal of Venomous Animals and Toxins Including Tropical Diseases, v. 24, 2019.5
7. CERVEIRA, M.; VIANNA, H.; FERRER, E.; DA ROSA, B.; DE PEREIRA, C.; BALDISSERA, M.; LOPES, L.; RECH, V.; GIONGO, J.; VAUCHER, R. Bioprospection of novel synthetic monocurcuminoids: Antioxidant, antimicrobial, and in vitro cytotoxic activities. Biomedicine & Pharmacotherapy, v. 133, p. 111052, 2021.
8. CONLON, J.; ATTOUB, S.; ARAFAT, H.; MECHKARSKA, M.; CASEWELL, N.; HARRISON, R.; CALVETE, J. Cytotoxic activities of [Ser49] phospholipase A2 from the venom of the saw-scaled vipers Echis ocellatus, Echis pyramidum leakeyi, Echis carinatus sochureki, and Echis coloratus. Toxicon, v. 71, p. 96-104, 2013.
9. CÔRREA, E.; KAYANO, A.;DINIZ-SOUSA, R.; SETÚBAL, S.; ZANCHI, F.; ZULIANI, J.; MATOS, N.; ALMEIDA, J.; RESENDE, L.; MARANGONI, S.; SILVA, S.; SOARES, A.; CALDERON, L. Isolation, structural and functional characterization of a new Lys49 phospholipase A2 homologue from Bothrops neuwiedi urutu with bactericidal potential. Toxicon, v. 115, p. 13-21, 2016.
10. CHIEN-CHIHN, C.; KUEI-LI, L.; CHING-MING, C.; LONG-SEN, C.; SHINNE-REN, L. Effects of Cardiotoxin III on NF- B Function, Proliferation, and Apoptosis in Human Breast MCF-7 Cancer Cells. Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics, v. 17, n. 7, p. 311-321, 2009.
11. FRIHLING, B.; BOLETI, A.; de OLIVEIRA, C.; SANCHES, C.; CARDOSO, P.; VERBISCK, N.; MACEDO, M.; RITA, P.; CARVALHO, C.; MIGLIOLO, L. Characterization and Evaluation of the Antitumoral Activity of a Phospholipase A2 from the Snake Bothrops moojeni. Pharmaceuticals, v. 15, n. 6, p. 724, 2022.
12. GEBRIM, L.; MARCUSSI, S.; MENALDO, D.; MENEZES, C.; NOMIZO, A.; HAMAGUCHI, A.; SILVEIRA-LACERDA, E.; HOMSI-BRANDEBURGO, M.; SAMPAIO, S.; SOARES, A.; RODRIGUES, V. Antitumor effects of snake venom chemically modified Lys49 phospholipase A2-like BthTX-I and a synthetic peptide derived from its C-terminal region. Biologicals, v. 37, n. 4, p. 222-229, 2009.

13. ISHIKAWA, T.; WONDIMU, Z.; OIKAWA, Y.; GENTILCORE, G.; KIESSLING, R.; BRAGE, S.; HANSSON, J.; PATARROYO, M. Laminins 411 and 421 differentially promote tumor cell migration via $\alpha 6\beta 1$ integrin and MCAM (CD146). Matrix Biology, v. 38, p. 69-83, 2014.
14. JAYATILLEKE, K.; HULLET, M. Heparanase and the hallmarks of cancer. Journal of Translational Medicine, v. 18, n. 1, p. 1-25, 2020.
15. HEBERT, S.; ODELL, A.; PONNAMBALLAM, S.; WALKER, J. Activation of Cytosolic Phospholipase A2-{Alpha} as a Novel Mechanism Regulating Endothelial Cell Cycle Progression and Angiogenesis. Journal of Biological Chemistry, v. 284, n. 9, p. 5784-5796, 2009.
16. JIMÉNEZ-CHARRIS, E.; LOPES, D.; GIMENES, S.; TEIXEIRA, S.; MONTEEALEGRE-SANCHEZ, L.; SOLANO-REDONDO, L.; FIERRO-PEREZ, L.; ÁVILA, V. Antitumor potential of Pllans–II, an acidic Asp49–PLA2 from Porthidium lansbergii lansbergii snake venom on human cervical carcinoma HeLa cells. International journal of biological macromolecules, v. 122, p. 1053-1061, 2019.
17. JOHNSON, P.; GREINER, W.; AL-DAKKAK, I.; WAGNER S. Which Metrics Are Appropriate to Describe the Value of New Cancer Therapies? Biomed Research International. v. 2015, 2015.
18. KATO, E.; PIMENTA L.; de ALMEIDA, M.; ZAMBELLI, V.; dos SANTOS, M.; SAMPAIO S. Crotoxin inhibits endothelial cell functions in the two-and three-dimensional tumor microenvironment. Frontiers in Pharmacology, p. 1998, 2021.
19. KATO, E.; SAMPAIO, S. Crotoxin modulates events involved in epithelial–mesenchymal transition in 3D spheroid model. Toxins, v. 13, n. 11, p. 830, 2021.
20. LAZCANO-PÉREZ, F.; RANGEL-LÓPEZ, E.; ROBLES-BANUUELOS, B. FRANCO-VÁZQUEZ, A.; GARCÍA-ARREDONDO, A.; NAVARRO-GARCÍA, J.; ZAVALA-MORENO, A.; GÓMEZ-MANZO, S.; SANTAMARIA, A.; ARREGUÍN-ESPINOSA, R. Chemical structure of three basic Asp-49 phospholipases A2 isolated from Crotalus molossus nigrescens venom with cytotoxic activity against cancer cells. Toxicon, v. 210, p. 25-31, 2022.
21. LEE, H.; PARK, M.; SON, D.; SONG, H.; KIM, J.; KO, S.; SONG, M.; LEE, W.; YOON, J.; HAM, Y.; HAN, S.; HONG, J. Anticancer effect of snake venom toxin through down-regulation of AP-1 mediated PRDX6 expression. Oncotarget, v. 6, n. 26, p. 22139, 2015.
22. MANGUIKIAN, A.; BARBOUR, J. Role of extracellular vesicles during oocyte maturation and early embryo development. Journal of Biological Chemistry, v. 279, n. 51, p. 52881-52892, 2004.
23. MIRAN, J.; YUN, H.; PARK, K.; PARK, M.; KIM, T.; PAK, J.; LEE, S.; MOON, D.; PARK, C.; SONG, S.; LEE, C.; HAN, S.; HONG, J. Lung tumor growth-promoting function of peroxiredoxin 6. Free Radical Biology and Medicine, v. 61, p. 453-463, 2013.
24. MOURA, G.; MONTEIRO, P. Cytotoxic Activity of Antineoplastic Agents on Fertility: A Systematic Review. Revista Brasileira de Ginecologia e Obstetrícia. v. 42, p. 759-768, 2020.
25. MOURA, G.; OLIVEIRA, J.; ROCHA, Y.; OLIVEIRA, J.; RODRIGUES, J.; FERREIRA, V.; NICOLETE, R. Antitumor and antiparasitic activity of antimicrobial peptides derived from snake venom: a systematic review approach. Current Medicinal Chemistry, 2022.
26. MULLER, S.; SILVA, V.; SILVESTRINI, A.; MACEDO, L.; CAETANO, G.; REIS, R.; MAZI, M. Crotoxin from Crotalus durissus terrificus venom: In vitro cytotoxic activity of a heterodimeric phospholipase A2 on human cancer-derived cell lines. Toxicon, v. 156, p. 13-22, 2018.
27. NELSON, J.; BARLOW, K.; BECK, D.; BERBERT, A.; ESHENRODER, N.; FRANCON, L.; PRITT, M.; THOMPSON, K.; THOMPSON, K.;THURBER, B.; YEUNG, C.; JUDD, A. Synergistic effects of secretory phospholipase A2 from the venom of Agkistrodon piscivorus piscivorus with cancer chemotherapeutic agents. BioMed Research International, v. 2013, 2013.
28. OJEDA, P.; RAMÍREZ, D.; ALZATE-MORALES, J.; CABALLERO, J.; KAAS, Q.; GONZALEZ, W. Computational studies of snake venom toxins. Toxins, v. 10, n. 1, p. 8, 2017.
29. PEGGION, C.; TONELLO, F. Short linear motifs characterizing snake venom and mammalian phospholipases A2. Toxins, v. 13, n. 4, p. 290, 2021.
30. SALES, T.; MARCUSSI, S.; CUNHA, E.; KUCA, K.; RAMALHO, T. Can inhibitors of snake venom phospholipases A2 lead to new insights into anti-inflammatory therapy in humans? A theoretical study. Toxins, v. 9, n. 11, p. 341, 2017.
31. SOUSA, I.; BARBOSA, A.; SALVADOR, G.; FRIHLING, B.; SANTA-RITA, P.; SOARES, A.; PESSÔA, H.; MARCHI-SALVADOR, D. Secondary hemostasis studies of crude venom and isolated proteins from the snake Crotalus durissus terrificus. International Journal of Biological Macromolecules, v. 131, p. 127-133, 2019.
32. VIEIRA, L.; MAGRO, A.; FERNANDES, C.; DE SOUZA, B.; CAVALCANTE, W.; PALMA, M.; ROSA, J.; FULY, A.; FONTES, M.; GALLACI, M.; BUTZKE, D.; CALDERON, L.; STÁBELI, R.; GIGLIO, J.; SOARES, A. Biochemical, functional, structural, and phylogenetic studies on Intercro, a new isoform phospholipase A2 from Crotalus durissus terrificus snake venom. Biochimie, v. 95, n. 12, p. 2365-2375, 2013.
33. WANG, J.; LEI, K.; HAN, F. Tumor microenvironment: recent advances in various cancer treatments. European Review for Medical and Pharmacological Sciences. v. 22, p. 3855-3864, 2018.
34. WHO. World Health Organization. Cancer. Available on: <https://www.who.int/health-topics/cancer#tab=tab_1>. Accessed on June 4th, 2022.

35. XIE, C.; BITTENBINDER, M.; SLAGBOOM, J.; ARRAHMAN, A.; BRUIJNS, S.; SOMSEN, G.; VONK, F.; CASEWELL, N.; GARCÍA, J.; KOOL, J. Erythrocyte haemotoxicity profiling of snake venom toxins after nanofractionation. Journal of Chromatography B, v. 1176, p. 122586, 2021.
36. YAN, C.;QIN, Z.; GU, Z.; REID, P.; LIANG, Z. Autophagy is involved in cytotoxic effects of crotoxin in human breast cancer cell line MCF-7 cells. Acta Pharmacologica Sinica, v. 28, n. 4, p. 540-548, 2007.