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Review - Biological and Applied Sciences

Studies about Snake Peptides: a Review about Brazilian Contribution

Rhayane Alves Assis[1,2*]
https://orcid.org/0000-0001-6750-5490

Elaine Divina Rodrigues Silveira[1]
https://orcid.org/0000-0002-1697-7436

Bruno Barros Bittar[3,4]
https://orcid.org/0000-0002-8956-3525

Marcelino Benvindo-Souza[1,3]
https://orcid.org/0000-0001-9008-6087

Nathan Pereira Lima Amorim[1]
https://orcid.org/0000-0003-4459-3242

Lia Raquel de Souza Santos[1]
https://orcid.org/0000-0003-3700-813X

Guilherme Henrique Carrasco[1]
https://orcid.org/0000-0002-6284-9750

[1]Instituto Federal Goiano, Laboratório de Ecotoxicologia e Sistemática Animal, Rio Verde, Goiás, Brasil; [2]Universidade Estadual Paulista "Júlio de Mesquita Filho", Instituto de Biociências, Letras e Ciências Exatas, Departamento de Biologia, Laboratório de Anatomia Comparada, São José do Rio Preto, São Paulo, Brasil; [3]Universidade Federal de Goiás, Instituto de Ciências Biológicas, Laboratório de Mutagênese, Goiânia, Goiás, Brasil; [4]Instituto Federal Goiano, Laboratório de Ecologia, Evolução e Sistemática de Vertebrados, Rio Verde, Goiás, Brasil

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*Correspondence: rhayanealves1@hotmail.com; Tel.: +55-64-984235478 (R.A.A.).

HIGHLIGHTS

- Brazilian scientific production on snake peptides has grown over the years.
- São Paulo, is the most representative state in Brazil in research.
- The main periodical where researches were published, is the Toxicon journal.
- Collaboration is observed between institutions in Brazil and other countries.

Abstract: The peptides present in snake venoms are studied because of their properties, constitutions, mechanisms of action and pharmacological potential. Recognizing this potential, the present study reports the contributions of Brazilian researchers about snake peptides, between 1975 and July 2020. Thus, this study serves as a basis for monitoring this theme in Brazil, referring to the trends and patterns of scientific production. The results indicated a significant increase in Brazilian scientific production over the years, highlighting institutions located in São Paulo state as, the Butantan Institute and University of São Paulo. The main journal where Brazilian authors publish their research is the Toxicon Journal. Collaborative networks were identified between Brazilian institutions and among other countries with Brazil. The most investigated species are found in brazilian territory, mainly those belonging to the genus *Bothrops* and the species *Crotalus durissus*. The increase in studies about this theme in Brazil is evident, however, a gap is highlighted for states outside the southeastern region and for other venomous species.

Keywords: Biodiversity; Bioprospecting; Brazil; Reptiles; Scientific trend.

INTRODUCTION

Snake poisons are mixtures of proteins and peptides with several biological activities [1]. The toxins present in these compounds have pharmacological efficacy, especially antibacterial, considering the evidence observed in several studies [2-3]. Drugs produced from the active ingredients of snake toxins can be used to treat various diseases, including cardiovascular and cancer, as well as a pain relief and skin care [4-5]. The crotamine peptide, found in snakes from genus *Crotalus*, performs a series of biological functions, such as antimicrobial and antitumor [6]. It has also been reported that peptides extracted from *Bothrops jararaca* (Wagler 1824) were able to reduce blood pressure and improve renal function in hypertensive animals [7].

The snake venoms composition varies according to factors such as gender, family, species, geographic location, type of prey, age and size of the individual [8-9]. Techniques called "omics", such as proteomics and transcriptomics, have enabled the understanding of the biochemistry and functionality of poisons, as well as their application in biotechnology, allowing the use of these poisons from drug development to agricultural application [10-11]. In Brazil, there are 392 species of snakes [12] found in many habitats and niches [13]. In Brazil, researches were carried out and discovered the bradykinin in *B. jararaca* venom in 1949 [14] and, later, bradykinin-potentiating peptides in the 1960s [15], that allowed the creation of the drug captopril [16] used to treat arterial hypertension. The Butantan Institute is the main immunobiological producer in the country, developing diverse projects about composition and action of snake venoms and assisting in the new drugs development, according to the official website of the institute (https://butantan.gov.br/institutional/o-instituto).

Researches about snake peptides as pharmacological agents, especially in developing countries such Brazil, are important, since in these countries infectious diseases are a major cause of death due to the indiscriminate use of antibiotics [17]. Thus, antimicrobial peptides from snakes have been studied as an alternative treatment to these diseases, since they have already demonstrated efficacy against fungi [6, 18] and bacteria [17,19].

In this sense, the objective of this study was to track the scientific production in Brazil about peptides from snake venoms, to evidence (i) the time trend of papers produced in the country from the most remote year of the databases until July 2020; (ii) the geographic aspect of studies in the country; (iii) the institutions to which the authors and co-authors of these studies were linked; (iv) the journal where these papers were published; (v) collaboration networks between institutions; (vi) the countries which Brazilian researchers had partnerships and (vii) the main species studied.

MATERIAL AND METHODS

Data collection

In this study, was reviewed the literature that addresses snake peptides published by researchers (including first authors and co-authors) linked to Brazilian institutions until July 2020. The full articles, reviews and short communications were searched on the ISI Web of Science and Scopus databases with the keywords: “snakes” and “peptides”. Papers that did not address snake peptides, whose authors institutions were not located in Brazil, and in which the complete paper was not found were discarded.

For each paper found were investigated: (i) the year of publication, (ii) geographic aspect of the research (state of the country where the educational institution whose Brazilian authors and/or co-authors were linked during the execution of the research (iii) the institutions to whose Brazilian authors and/or co-authors were linked during the execution of the research, (iv) the journals in which the papers were published, (v) the collaborations between different institutions in the studies (vi) the collaborations of authors and/or co-authors linked to institutions in other countries and (vii) the investigated species of snakes.

Data analysis

The increase of published papers was calculated using Pearson's correlation coefficient ($p < 0.05$) between year and number of published articles. The data of Brazilian states and institutions that most contributed, as well as the journals where Brazilian’s scientists most published, are shown in the form of proportion. Collaboration networks between Brazilian institutions and among other countries with Brazil were built using the VOSviewer software. To analyze collaboration between institutions, the minimum number of documents by organization was four collaborations. To analyze collaboration between countries, the minimum number of publications by country was one. Because of the divergence in the way that the names of institution are written in papers, the names of the institutions were unified.

RESULTS

Temporal and geographical aspect

The search on the Web of Science returned 2209 papers published since 1967. The Scopus database returned 5367 documents published since 1952. Considering the two databases, 592 studies had the participation of researchers linked to Brazilian institutions. After evaluating the criteria, 451 were selected for data analysis. Among these, researchers from Brazilian institutions were the main authors in approximately 84% of the studies (n = 380) and co-authors, led by foreigners, in approximately 15% (n = 71). The first paper found, according to the criteria, dates to 1975, increasing until July 2020 ($r = 0.91$; $p < 0.001$; Figure 1). Scientific collaboration was registered in institutions in 20 states in Brazil, out of 27 in the country (Figure 2). Considering the regions of all authors, the most representative institutions are located mainly in the state of São Paulo, which has been the driving force with approximately 72% of the studies (n = 326), followed by Minas Gerais 17% (n = 78) and Rio de Janeiro, whose institutions contributed with 13% (n = 60). The others Brazilian states contributed with about 6.19% (n = 28) of total production.

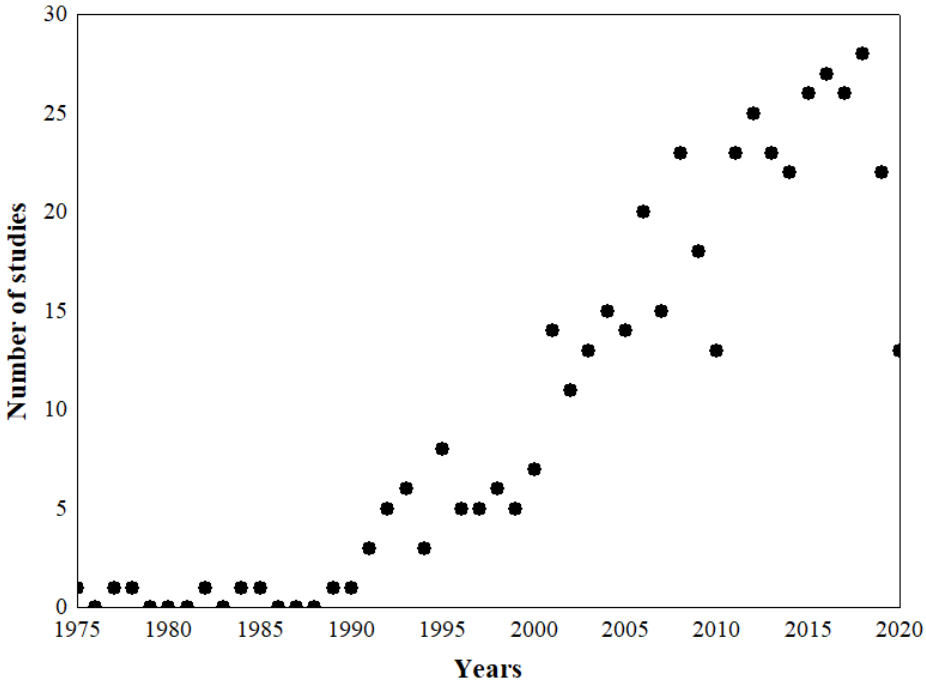

Figure 1. Number of published papers about snake peptides with the participation of Brazilian researchers between 1975 and July 2020.

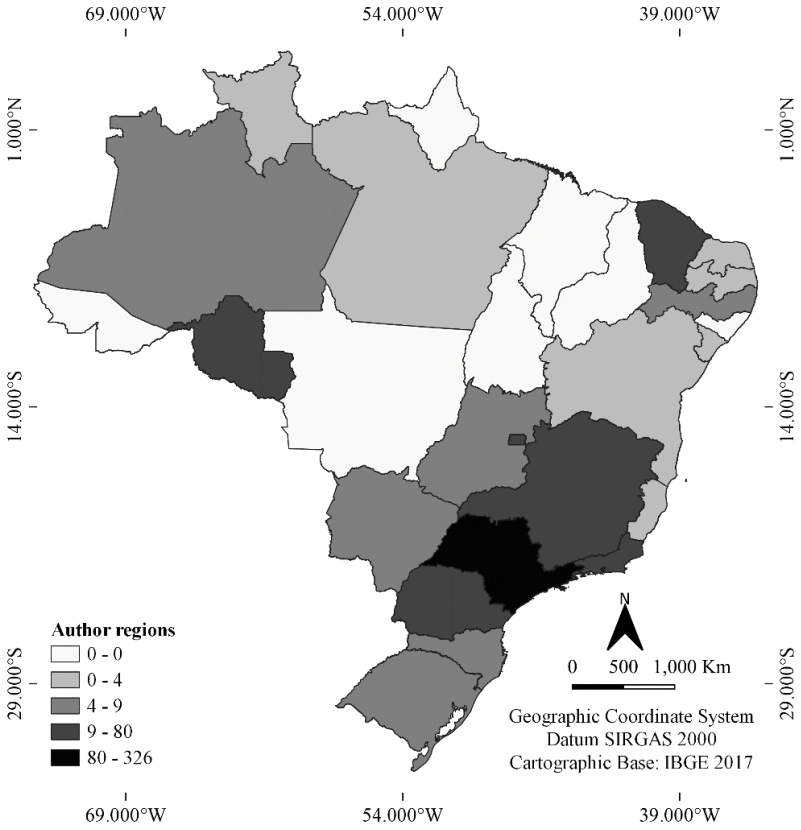

Figure 2. Representativeness of the Brazilian states' contribution in studies about snake peptides.

Main institutions, journals and collaboration networks

The contribution of 91 Brazilian institutions in the papers was recorded. More than 40% of the 451 papers had the participation of Butantan Institute (n = 184). Two other representative institutions were the University of São Paulo (USP) with 30% (n = 137) and the Federal University of São Paulo (UNIFESP) with 13% (n = 60). It is also important to highlight other Brazilian institutions such as the State University of São Paulo "Júlio de Mesquita Filho" (UNESP) (n = 49) and the State University of Campinas (UNICAMP) (n = 40), as well as the Oswaldo Cruz Foundation (FIOCRUZ) (n = 38), the Ezequiel Dias Foundation (FUNED) (n = 36), the Federal University of Rio de Janeiro (UFRJ) (n = 32), the Federal University of Minas Gerais (UFMG) (n = 28) and the Federal University of Ceará (UFC) (n = 24). The other institutions together (n = 81) accounted for about 67% of the papers (n = 303).

The 451 researches were published in 127 journals, whose Toxicon journal holds the largest number of papers, 24.8% (n = 112). Next are the journals, Comparative Biochemistry and Physiology with 4.4% (n = 20), Journal of Venomous Animals and Toxins Inclusing Tropical Diseases with 4.2% (n = 19), Journal of Proteomics (3.5%, n = 16), Toxins (3.5%, n = 16), Archives of Biochemistry and Biophysics (2.8%, n = 13), Biochimie (2.8%, n = 13), Peptides (2.8%, n = 13), Journal of Proteome Research (2.6%, n = 12) and Biochimica et Biophysica Acta (2.4% n = 11). Other journals together account for about 45% (n = 206).

Several collaboration networks were observed between institutions in Brazil (Figure 3), as well as the collaboration of institutions outside the country, such as the United States, Germany, Japan, France and Spain (Figure 4).

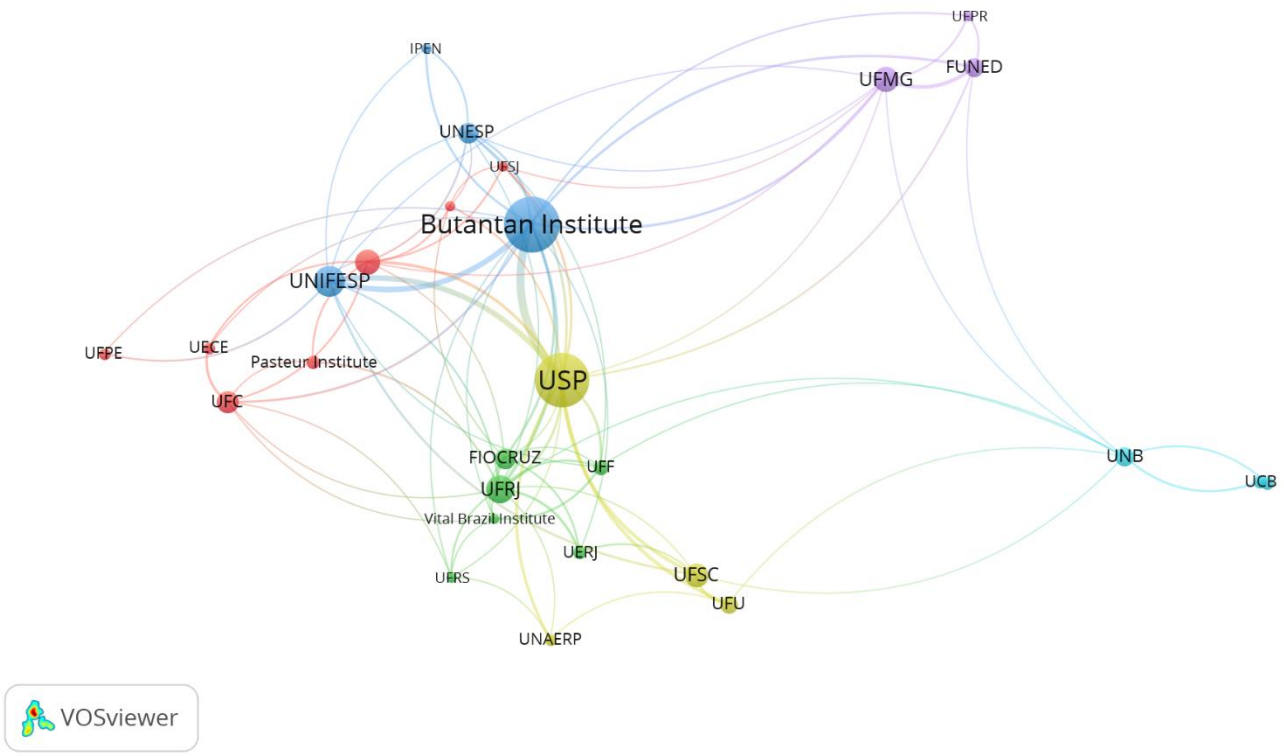

Figure 3. Collaboration network between Brazilian institutions involved in studies about snake peptides. Federal University of Pernambuco (UFPE), State University of Ceará (UECE), Federal University of São João del-Rei (UFSJ), Institute for Energy and Nuclear Research (IPEN), Federal University of Rio Grande do Sul (UFRS), State University of Rio de Janeiro (UERJ), University of Ribeirão Preto (UNAERP), Federal University of Santa Catarina (UFSC), Federal University of Uberlândia (UFU), Federal University of Paraná (UFPR), Univesity of Brasília (UNB), Catholic University of Brasília (UCB).

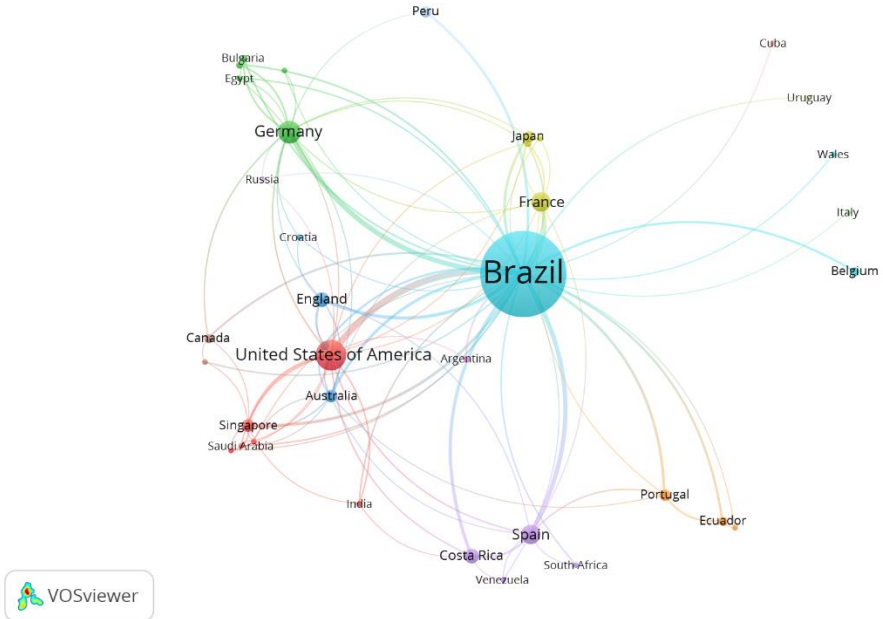

Figure 4. Collaboration among between Brazil and other countries in studies about snake peptides.

Species investigated

A total of 92 species were investigated in different studies involving the antibacterial, antihypertensive, antifungal, antitumor potential, as well as its use for antiophidic serum production and its peptides. About 25% (n = 116) of the papers evaluated the *Bothrops jararaca* species, while approximately 21% (n = 96) studied *Crotalus durissus* (Linnaeus 1758) and 7% (n = 33) used *Bothrops jararacussu* (Lacerda 1884). Considering that many studies used more than one species, other species were investigated in 79.15% of

the papers (n = 357). Approximately 9.31% (n = 42) of the papers did not specify the used species or were review papers. Table 1 shows the number of studies with the most cited species.

Table 1. Most investigated snake species in studies on peptides published with the collaboration of Brazilian.

Species	Number of studies
Bothrops jararaca	116
Crotalus durissus	96
Bothrops jararacussu	33
Bothrops atrox	28
Lachesis muta	24
Bothrops alternatus	22
Bothrops moojeni	22
Bothrops insularis	14
Bothrops neuwiedi	14
Bothrops leucurus	10
Agkistrodon contortrix	8
Bothrops erythromelas	8
Bothrops asper	7
Bothrops brazili	6
Bothrops cotiara	6
Agkistrodon piscivorus	5
Bothrops pirajai	5
Crotalus oreganus abyssus	5
Bitis arietans	4
Bothrops pauloensis	4
Vipera ammodyles	4
Bitis rhinoceros	3
Bothrops lanceolatus	3
Bothrops pictus	3
Calloselasma rhodostoma	3
Crotalus atrox	3
Crotalus viridis	3
Daboia russelii	3
Atropoides nummifer	2
Bitis gabonica	2
Bitis nasicornis	2
Bothrops mattogrossensis	2
Echis carinatus	2
Trimeresurus flavoridis	2

DISCUSSION

Temporal and geographical aspect

The first study found in the databases dates from 1975 and it evaluated bradykinin-potentiating peptides in the venom of *B. jararaca* and *Gloydius blomhoffii* (Boie 1826) (referred in the article as *Agkistrodon halys blomhoffii*), being the latter, geographically distributed in Japan, China and Russia. The study evaluated the relationship between the structure and activity of synthetic peptides in guinea pig (*Cavia porcellus*) and in female rats [20]. From then on, until the 1990s, few studies were published by Brazilian researchers, most of them linked to the Butantan Institute and USP using the species *B. jararaca* [21-22]. An increase in the number of papers begins to be observed from 1990 when the first works of researchers linked to institutions of Goiás [23], Minas Gerais [24], Rio de Janeiro [25] and Rio Grande do Sul states [26] were published. Among the papers published in this decade, there is a study with the poison of *C. durissus*, with the crotoxin purification [27], and with the crotamine potential to act as an analgesic [28].

The increase in the number of papers with the collaboration of Brazilians is more evident in the 2000s. Until the beginning of the decade, the peptides from coral snake (*M. corallinus*) venom had been little studied. Brazilian researchers have contributed to the reduction of this gap by analyzing, cloning and characterizing components of the toxins of this species, including peptides [29-30]. There are also studies that have identified new bradykinin-potentiating peptides in the venom of *B. jararaca* [31] and studies that used these peptides to develop drugs against hypertension, since bradykinin is involved in blood pressure control and other physiological processes [32]. In addition, Gomes and coauthors [33] isolated a new peptide from the snake *B. jararaca* with inhibitory function against phytopathogenic fungi like *Fusarium oxysporum* and *Colletotrichum lindemuthianum* and yeasts like *Candida albicans* and *Saccharomyces cerevisiae*.

Rizzi and coauthors [34] demonstrated that the crotamine from *C. durissus* poison preferentially inhibits fast muscles, however, the authors claim that the sodium channels would not be the targets of this peptide toxin, as was believed before. Regarding bradykinin-potentiating biomolecules, Rioli and coauthors [35] identified a new *B. jararacussu* peptide with the potential to induce arterioles vasodilation with little increase in leukocyte flow. Cardoso and coauthors [36] found peptides with immunogenic activity against toxins from the snake venom of *B. neuwiedi*, contributing with another possibility of protection in case of poisoning by that snake. In addition to these works, Martins and coauthors [37] studying the *B. atrox* venom, detected peptides with neuroprotective function acting against mitochondrial swelling in the brain of rats, contributing to strategies for treatment against neurodegenerative diseases.

In the last decade, there has been a significant participation of Brazilian institutions in the studies found. Among them, the study by Martins-Santos and coauthors [38] investigated the effect of a mixture of peptides from *C. durissus* on glucose concentration in rats fed a high-fat diet and showed a reduction in glycemia as well as in the glucose concentration in blood. Silva and coauthors [39] isolated and characterized a peptide from *Crotalus oreganus* showing its properties in the blood pressure regulation. A study with *Bothropoides mattogrosensis* venom, detected peptide fragments with anti-microbial activity in the enzyme L-amino oxidase, suggesting these as candidates for new antibiotic projects [40]. Another study with bradykinin-potentiating peptides from *B. jararaca*, showed that they induce morphological changes in the seminiferous tubules of rats, impairing spermatogenesis, however, the same was not observed when the animals were exposed to the captopril medication, derived from these peptides [41]. Martins and coauthors [42] isolated a peptide from *B. atrox* venom with neuroprotective activity that can be effective as a therapeutic strategy for Parkinson's disease.

Dal Mas and coauthors [43] reported that in addition to antimicrobial and antitumor activity, crotamine has unique cell penetrating properties with affinity for acidic vesicles, and anthelmintic potential, proposing a way to overcome drug resistance. Cavalcante and coauthors [44] detected antifungal activity of *C. durissus* crotalicidine, pointing out that it is a promising clue for treatment of fungal diseases. One year later, Bandeira and coauthors [45] found that crotalicidine has an effect against Chagas disease, contributing to the possible development of agents against this disease. More recently, a study with *B. moojeni* snake identified a peptide derived from a metalloprotease with an inhibitory action on the survival of *Plasmodium falciparum*, that causes malaria [46]. In addition, Oliveira and coauthors [47] described the antimicrobial activities against a diversity of microorganisms, the action modes and structure of new peptides from *C. durissus*. It is important to highlight that, over the years, studies by Brazilian researchers have also shown that the study of the composition of snake venoms, including peptides, can be applied beyond pharmacology, for example, to understand the evolutionary relationships between different snake species and their distribution pattern throughout evolution [48]. About these applications, currently, the development of biopesticides for agricultural use from snake venom has also been studied [11]. It is important to highlight that proteomics techniques were used in most studies, that is, venom components such as proteins and peptides were separated, identified and characterized through techniques such as chromatography, electrophoresis and phylogenetic analysis [49-50]. The knowledge gained from the use of proteomics (and other approaches such as genomics) allows the development of biotechnology from biological resources such as snake venoms to create more sustainable solutions for agriculture such as new crop varieties and biopesticides [11].

Most of the studies had the collaboration of at least one author linked to institutions located in São Paulo, which mean that the five institutions that most contributed to studies are located in this state. This tendency of scientific production in Brazil to be concentrated in the southeast region has been pointed out by reviews published in several areas such as health and biological sciences [51-52], dentistry [53], education [54], renewable energies [55] and pharmaceutical care [56]. According to a study by the Industries Federation of Ceará State (FIEC) in 2018, São Paulo is the state of Brazil that is in the first place in the ranking of capabilities that most invest in infrastructure and communications, public investment in science and technology, quality of graduate studies and insertion of masters and doctors in the industry. At the same time, the state ranks second in the index that considers scientific publications, global competitiveness in

technological sectors, technological intensity of the productive structure and intellectual property in industry. The survey shows, therefore, that São Paulo state is a leader in public investment in science, followed by other states in the southeastern region such as Rio de Janeiro and Minas Gerais that occupy the fourth and seventh place, respectively. In the south region are Paraná and Rio Grande do Sul, which occupy, respectively, the second and fifth place, while the Federal District, in the central-west region, occupies the third position of the ranking. It is also important to note that São Paulo is the state with the highest gross national product (GNP) in the country according to IBGE (Brazilian Institute of Geography and Statistics) and that, historically, there has been a continuous investment in research and development, which can explain the concentration of scientific production in that state [52].

Main institutions, journals and collaboration networks

The Butantan Institute, a leader in contributing to studies in Brazil, is an institution that was born in 1901 in the state of São Paulo with to produce serum against bubonic plague [57]. Over the years, the institute has become one of the main scientific institutions in Brazil, known worldwide for studying the toxins of venomous animals, in addition to projects related to vaccines production, which attracted the attention of several international institutions for establishment of partnerships [57]. In relation to snakes, from the research carried out by the institution, various serums are produced, such as antibotropic, anticrotalic and antielapidic, which are made available to the population free of charge through the Health Ministry (see the Institute's website). In addition, the Butantan Institute is made up of 35 scientific laboratories, a center for technological innovation, a hospital specializing in treating victims of accidents with venomous animals, animal houses for snakes and other venomous animals and a team of researchers, including professionals, masters, doctoral and postdoctoral students [58].

Thus, the research demonstrates the importance of the institution in Brazilian scientific production, contributing from the first studies found in the databases to the most recent ones. Among them, there are studies about constitution, characterization and therapeutic potential of components from venom of *B. jararaca* [21-22, 58-60], *C. durissus* [34, 61-64] among several other snake species.

Another significant institution that collaborate with studies is the University of São Paulo, USP. According to the 2019 Clarivate Analytics company report, USP is the most productive Brazilian university in all sectors of science (Health Sciences, Biological Sciences, Exact and Natural Sciences, Agricultural Sciences and Engineering), followed by UNESP and UNICAMP. Historically, greater investment in research has been observed through public and private sectors in São Paulo, in addition to the presence of an important development agency, the São Paulo State Research Support Foundation (FAPESP), which have been pointed as the justification for concentrated scientific production in São Paulo universities [51]. Other important health institutions in Brazil were FIOCRUZ and FUNED. Among its lines of research, FIOCRUZ has studies related to toxicology and the production of antibiotics, anti-inflammatories, analgesics, in addition to medicines for diseases of nervous system, hypertension and diabetes, according to the official website of the institution. FUNED is also one of the references in the research of snake venoms in Brazil. Regarding patent registrations, a search of the EPO patent database (worldwide.espacenet.com) shows that researchers from the Federal University of São Carlos, FAPESP and the UERJ have patented synthetic peptide derived from alternagin-C of *B alternatus*, other patent records are found for FIOCRUZ (combination of crotamine from *C. durissus* and drugs for the treatment of leishmaniasis), for UFMG with the use of formulation containing crotoxin for the treatment of muscle dystonias, among other records.

In relation to the journals where the researches were published, there is a large volume of papers in the Toxicon Journal. This journal, currently with an impact factor of 2.201, aims to publish papers related to toxins from animals, plants and microorganisms, in particular chemical, pharmacological, toxicological and immunological properties of these toxins, in addition to clinical observations on poisoning. These papers had focus on antibacterial, antitumor and analgesic activities, among others. Also, at the time of this research, this journal accepts full research articles, short communications, letters to the editor, announcements, reviews, mini-reviews and clinical reports. Among the studies published in this journal, there are works dating from the 1980s, featuring components of the *B. jararaca* venom [22], hemorrhagic factors of *B. neuwiedi* [65], a study with the snake *B. moojeni* [66] and evaluation of *Naja naja* peptide [67]. Over the years, papers have been published evaluating the venom hemorrhagic factors of the snake *Lachesis muta* [68], the renal toxicity of the venom from *B. moojeni* snake [69], the action mechanisms of crotamine peptide [34] and the urinary metabolites of *B. jararaca* bradykinin-potentiating peptides in mice [70]. More recently, there is a study about the poison of *B. jararaca* [71], in addition to others.

Another important journal pointed out is Comparative Biochemistry and Physiology, a journal divided between parts A (Molecular and Integrative Physiology), B (Biochemistry and Molecular Biology), C

(Toxicology and pharmacology) and D (Genomics and Proteomics). Most studies were published in part C of the journal (n = 10 studies, 50% of the total of 20 studies published in the journal). The scope of this journal is the toxicological mechanisms at different levels of organization, mainly molecular assessments of the xenobiotic's mechanisms of action on the organism physiology. Among the studies published by this journal are research about a new peptide in the poison of *C. durissus* [72], on endothelin, vasoactive peptides, and the differences in their receptors in B. jararaca and *Oxyrhopus guibei* snakes [73]. There was also great prominence in the work about vasoactive peptides isolated from *B. jararaca* plasma [74], a study about biochemical characterization of *Pseudoboa neuwiedii* venom [75] and the discovery of cardioprotective effects of alternagin-C, a peptide from *B. alternatus* snake [76].

As for collaboration networks, there are many works carried out in partnership by researchers from different Brazilian institutions. The Butantan Institute and USP show an expressive network of collaboration with institutions from different regions of Brazil. In addition to these, institutions such as UNIFESP, UFMG and UFRJ also showed interinstitutional partnerships. Partnerships between research institutes such as Vital Brazil Institute and Pasteur Institute and universities are noted. However, it is observed that the collaboration networks are predominantly formed by institutions located in the southeast region. These partnerships between researchers from different areas and institutions are important for science development in country, since they can assist to obtain faster results and, therefore, in the development of research [77].

Although collaboration networks have been observed in studies about snake peptides, the low participation of institutions in other regions should be considered. A similar result is pointed out by reviews that highlighted the collaboration between Brazilian researchers, showing a predominance of institutions located in the southeastern and southern regions [78]. As for international collaboration, Brazilian institutions have presented partnerships with researchers from several countries such as the United States, France, Germany, Japan, Costa Rica and Spain. International collaboration with Brazil has been evidenced in several areas of science [78-80] and demonstrates that this collaboration is a trend of Brazilian researchers.

Species investigated

Among the 11 species with more studies about their peptides, 8 belong to the genus *Bothrops*, popularly known as jararacas. The species of this genus are distributed throughout all regions of Brazil and, due to this wide distribution, encounters with humans are common, making these snakes responsible for almost 90% of snakebites in the country [81]. The *B. jararaca* species has been studied from 1975 to the present day in terms of bradykinin-potentiating peptides [20, 41, 82-86]. These peptides are antihypertensive molecules that inhibit the degradation of a hypotensive peptide and the formation of a vasoconstrictor peptide [87]. Other studies have evaluated antifungal peptides [33], pituitary neuropeptides [88] and have discovered new hypotensive peptides in the snake's plasma [73].

The antihypertensive activity of a proline-rich peptide (Bj-PRO-10c) isolated from the poison [89] has also been documented. This same peptide has been linked by Brazilian researchers to the normalization of endothelial dysfunction related to preeclampsia, which is a disease characterized by hypertension during pregnancy, that is, the peptide is useful as an antihypertensive in cases of preeclampsia and can be effective for new treatments against the disease [90]. Still about *B. jararaca* peptides rich in proline, the properties of Bj-PRO 7a were also investigated by Brazilian researchers [91]. The peptides called Bj-PROs are recognized for being inhibitors of the angiotensin-converting enzyme and having pharmacological action, which resulted in the antihypertensive drug, Captopril [92]. Brazilian researchers contributed to the knowledge about these peptides by also discovering that, in addition to lowering blood pressure, these peptides improve kidney function [7] and have anxiolytic and antidepressant effects in rats [93]. Studies with the species also evaluated the effects of bradykinin-potentiating peptides on the structure of the seminiferous tubules of rats [93-94].

Another species of the *Bothrops* genus that has been studied by researchers in Brazil, is *B. jararacussu*, widely distributed in Brazil and neighboring countries, whose researches date from 1992 with a study about the bradykinin-potentiating peptides that are also found in the poison of this species [95]. Over the years, new peptides of this class have been discovered [35], with the evaluation of the antitumor activity [93] and antibacterial activities against multi-resistant bacteria [17]. Studies with *B. atrox*, a snake that occurs in northern Brazil as well as other countries, have emerged more recently and bring information about the differences of the venom composition in the different stages of the animal's life [97]. In addition, the peptide functions of the species venom against mitochondrial swelling of the brain were considered, suggesting potential for neuroprotection [37]. There was also potential against chagal disease of the batroxicidin peptide found in this species since the peptide induced cell death in the *Trypanosoma cruzi* parasite [98]. Another study characterized batroxin I as a peptide with antitumor potential [99].

The *B. alternatus* species had its peptides studied on chemotactic activities and inhibition of chemotaxis induced by a disintegrin [100], a peptide that affects the proliferation of human vascular endothelial cells [101], in addition to the fragment purification of venom from this species [102]. For the species *B. moojeni*, a snake that also has a wide distribution in the Brazilian territory, new bradykinin-potentiating peptides were isolated [102], as well as, the renal toxicity of the poison was detected [69] and the anti-leishmania effect [104]. For this species, the difference in the venom composition between males and females has been demonstrated [105], as well as the identification of a new peptide derived from a metalloprotease with antimalarial action [46], among other works.

The species *B. insularis*, on the other hand, draws attention due to its restricted distribution to an island in São Paulo and, despite this, to be present in many studies on peptides. For the species, there are studies that isolated several bradykinin-potentiating peptides even in the 90s [106], which identified peptides and proteins expressed by the snake venom gland [107], in addition to a study that isolated the insulin-disintegrin involved in physiological processes of endothelial cells [108]. The species *B. neuwiedi* has also been the subject of a study that isolated and characterized bradykinin-potentiating peptides [16], and others that characterized the snake's venom in terms of proteins and peptides [109-110]. Finally, in relation to this genus, the species *B. leucurus* has been investigated over the years as to the composition of its venom [111-112].

For another genus, attention is drawn to the species *C. durissus*, a snake widely distributed throughout Brazil, which occupies the second position among the most evaluated by snake peptide researchers in the country. Studies by Brazilian researchers investigating the composition of the venom of this species since 1993 have been found in the databases [62]. Among the publications, we highlight the studies with crotamine peptide, which causes spasms in the skeletal muscles and paralysis in the hind limbs in mice, in addition to antibacterial, hemolytic and antitumor activity [63, 64, 113-115]. Over the years, papers has been found with purification of crotoxin inhibitor which is the main component of snake venom [27], as well as the action mechanism and the structure of another component of the species venom, convulxin, which causes cardiovascular and respiratory disorders [116-117], about peptides involved in anti-inflammatory activity [118] as bradykinin-potentiating [119] and, more recently, new peptides found in the *C. durissus* venom with antimicrobial activity have been characterized [47].

In addition to these, the species *L. muta* and *M. corallinus* were also highlights among the most studied. As for *L. muta*, bradykinin-potentiating peptides were identified [120-121], among many others. As for the species *M. corallinus*, attention was focused on natriuretic peptides, important in blood pressure homeostasis [122] and on strategies against snake poisoning [123-124], among other studies that helped to understand other venom components of this species. Finally, it is interesting to note that, despite the many partnerships with foreign researchers, the attention of Brazilian researchers has been focused on species occurring in the national territory and in neighboring countries. Over the years, much has been discovered about the venom composition of snakes that occur in the country, especially about peptides.

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