

## Global trend in research conducted on crotamine: a bibliometric analysis

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### ABSTRACT

This study investigates the multifunctionality of the crotamine (CTA) peptide, highlighting the need to elucidate research topics and promotes cooperation among publications, authors, countries, and funding agencies. A bibliometric analysis was carried out to gain insights into the scientific production of CTA, with Brazil emerging as a leader in authorship and funding for publications. This study aims to provide a comprehensive view of the publications related to CTA, distill the most critical research topics, and highlight pertinent issues to help researchers integrate new concepts into their studies. The Web of Science database was used to search for publications related to CTA toxin, and the VOS Viewer software was employed for bibliometric and visual analysis of countries/regions, authors, keywords, and funding agencies. 239 publications were identified using the term "crotamine" and 176 were selected based on the search criteria. The most significant publications are in Toxicology, Pharmacology, and Molecular Biology. Notable funding agencies include CNPq, FAPESP, and CAPES. The keywords "toxin", "venom", and "protein" emerged as the most common terms, indicating their importance in current research and their potential for continuous progression. The research recorded substantial growth in the last decade given the versatility of CTA, and the number of documents is expected to increase. To further explore and take advantage of the valuable features of this polypeptide, it is crucial to strengthen cooperation between countries and researchers.

**Keywords:** Crotamine. Bibliometric Analysis. Cell-penetrating peptides.

## Tendência global em pesquisas realizadas com crotamina: uma análise bibliométrica

### RESUMO

Este estudo investiga a multifuncionalidade do peptídeo crotamina (CTA), ressaltando a necessidade de elucidar temas de pesquisa e promover a cooperação entre publicações, autores, países e agências financiadoras. Foi realizada uma análise bibliométrica para obter insights sobre a produção científica sobre CTA, com o Brasil emergindo como líder em termos de autoria e financiamento para publicações. O objetivo deste estudo é oferecer uma visão abrangente das publicações relacionadas à CTA, destilar os tópicos de investigação mais críticos e destacar questões pertinentes para ajudar os investigadores a integrarem novos conceitos nos seus estudos. A base de dados Web of Science foi utilizada para busca de publicações relacionadas à toxina CTA, e o software VOS Viewer foi empregado para análise bibliométrica e visual de países/regiões, autores, palavras-chave e agências financiadoras. Foram identificadas 239

publicações utilizando o termo “crotamina” e 176 publicações foram selecionadas com base nos critérios de busca. As publicações mais significativas estão nas áreas de Toxicologia, Farmacologia e Biologia Molecular. Agências financiadoras de destaque incluem o CNPq, FAPESP e CAPES. As palavras-chave “toxina”, “veneno” e “proteína” surgiram como os termos mais comuns, indicando a sua importância na investigação atual e o seu potencial para progressão contínua. A investigação registrou um crescimento substancial na última década e, dada a versatilidade da CTA, espera-se que o número de documentos aumente. Para explorar e aproveitar ainda mais as características valiosas deste polipeptídeo, é crucial reforçar a cooperação entre países e investigadores.

**Palavras-chave:** Crotamina. Análise bibliométrica. Peptídeos de penetração celular.

## INTRODUCTION

The study of pharmacologically active compounds in snake venom has served as a prototype for developing new therapeutic agents. Snake venoms are rich in proteins and peptide toxins that have specificity for a wide range of tissue receptors, making them clinically challenging and scientifically fascinating, especially for drug design (WARREL, 2010). Captopril was the first animal toxin-based drug approved for human use in 1981 (BORDON et al., 2020).

Crotamine (CTA), a highly basic toxin of the South American rattlesnake *Crotalus durissus terrificus* venom, behaves as a cell penetrating peptide displaying a natural high specificity for actively proliferating cells (KERKIS et al., 2004).

It was found that it could be used for cancer treatment, as an *in vivo* theranostic agent, or even as a cell cycle marker (HAYASHI et al., 2008; YAMANE et al., 2013; NASCIMENTO et al., 2012), in addition to its antifungal potential (DAL MAS et al., 2019, YAMANE et al., 2013). In addition, oral (CAMPEIRO et al., 2018) antinociceptive and anti-inflammatory metabolic activities were found (MOREIRA et al., 2021). It has also shown improvement in amastigote inhibition when a combined approach of CTA and Glucantime is used to treat tegumentary leishmaniasis (VALENTIM-SILVA et al., 2022). Its role as a cell penetration peptide is also recognized (KERKIS et al., 2014; HAYASHI et al., 2012; DE CARVALHO PORTA.; CAMPEIRO; HAYASHI, 2022). Toxins exhibit a wide range of pharmacological activities; however, CTA stands out due to its high versatility in interacting with the most different molecular targets regulating unique cellular processes.

Kerkis et al., (2010) pointed out eight potential biotechnological applications of CTA: cell transfection and transduction, stem cell reprogramming, molecular diagnosis, molecular therapy, nanobiotechnology, and medicine. This myotoxin, therefore, presents

chemical, pharmacological, and biotechnological properties that aroused interest in the scientific community in its investigation.

New approaches are being developed in view of the low effectiveness of methods commonly used to treat infectious diseases, including cancer, among others. The inefficiency of treatments is shown through the potential for adverse effects, pharmacological resistance, and extremely high costs.

However, the interest of researchers in this toxin has progressively increased, given the inconveniences generated by outdated therapies. Researchers from several countries have published relevant studies, and Brazil is at the forefront regarding research with this polypeptide.

## **MATERIALS AND METHODS**

### ***Database***

Studies were collected from the WOS database. It included world-class indexes from the WOS Core Collection, including the Science Citation Index Expanded (SCIE), Social Sciences Citation Index (SSCI), Arts and Humanities Citation Index (A&HCI), and others.

### ***Software***

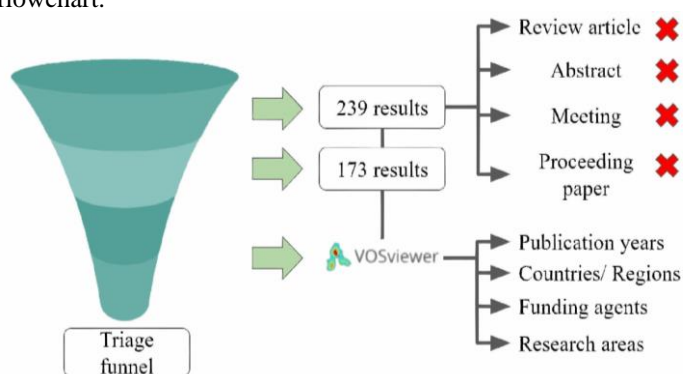
VOS Viewer is a software developed for constructing and visualizing bibliometric maps. The software is freely available to the bibliometric research community. VOS Viewer can, for example, be used to build author or journal maps based on cocitation data or to build keyword maps based on co-occurrence data. The program offers a viewer that allows bibliometric maps to be examined in detail (VAN ECK; WALTMAN, 2010).

### ***Inclusion criteria/exclusion criteria***

“Crotalid venoms”, “snake venoms”, “peptides” and “crotamine” were used as search terms according to the Medical Subject Headings (MeSH) database. To verify the existence of possible bibliometric analysis and CTA studies, the WOS Core Collection was used as a research tool. The terms “crotalid venoms” and “bibliometric analysis” were searched, and no articles were found. This bibliometric research is, therefore, the first related to the theme. Then, the search began using the search strategy shown in Figure 1. The search was carried out through the WOS Core Collection, the WOS platform

database through titles, abstracts, and keywords of scientific articles, in the English language, with the period of analysis (1957-2022) using the term "crotamine" to obtain the most significant number of researches related to the theme. A total number of 239 publications using the term "crotamine" were found by the WOS search site. Documents of the type of Article in the English language were selected and included in the study, totaling 176 publications that followed for bibliometric analysis (<https://www.webofscience.com/wos/woscc/summary/f8a604fa-6e80-460f-96fc-616f6bbf16d7-848a071c/relevance/1>).

**Figure 1 - Data sorting flowchart.**



### ***Exclusion criteria***

The following were excluded: 24 review articles and six publications in languages other than English, 28 of the Meeting Abstracts, 6 Proceeding Papers, 3 Notes, 1 of the Correction, and 1 of Early Access.

### ***Data extraction and analysis***

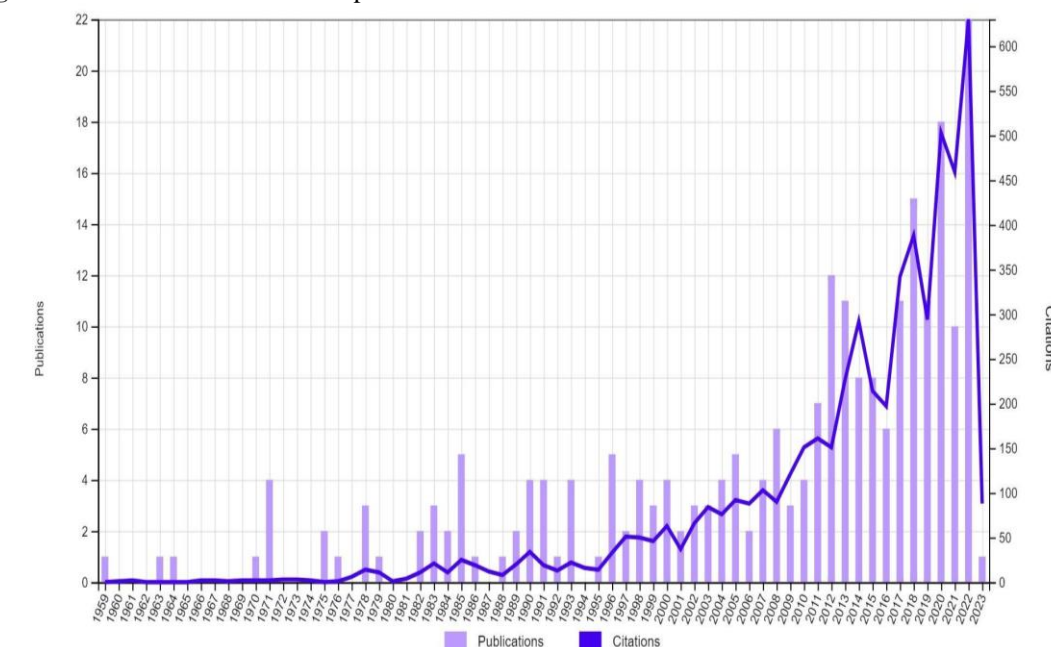
Given the results obtained, the WOS Clarivate Analytics tool was used to generate tree-type maps and bar graphs and describe indicators of category criteria, years of publication, authors, countries, languages, and research areas. Emphasis was given to the first ten items of each index, which contained the most considerable amounts of published works. Then, the WOS "Complete Record and Cited References" data was extracted in the txt file format and submitted to the VosViewer 1.6.16 software, which generated bibliometric networks in clusters format related to "co-authorship networks" by countries and "cocitation networks" and "keywords". It is important to emphasize that three patents use the CTA indexed in the Derwent Innovations Index. However, this study did not include them, as this database is not part of the primary WOS collection.

## RESULTS AND DISCUSSION

This myotoxin presents chemical, pharmacological, and biotechnological properties that aroused interest in the scientific community in its investigation (Figure 2).

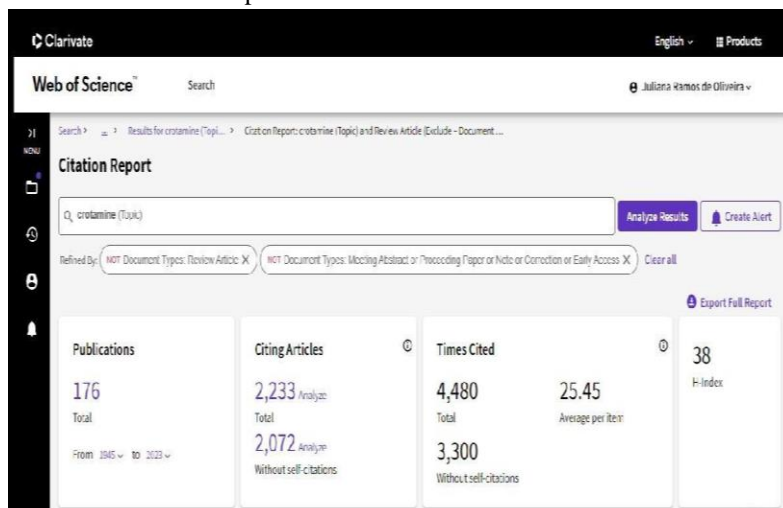
The terms “snake venoms” and “bibliometric analysis” generated four articles. Only one entitled "Bibliometric Analysis of Literature in Snake Venom-Related Research Worldwide (1933-2022) by Sofyantoro et al. (SOFYANTORO et al., 2022) drew attention, but the publication analyzes the global profile of the literature in snake venom research in the areas of antivenom, proteomics, and transcriptomes. With the terms "peptides” and “bibliometric analysis”, 37 articles resulted from the search, and none match the study proposed here.

**Figure 2** - Number of citations and publications over time.



Because of the data obtained from the WOS categories, graphs corresponding to the indexes used and mentioned in Figure 1 were generated. The bibliometric indicators researched for further analysis in VosViewer were the WOS category, year of publication, countries/regions, types of documents, research areas, authors, and keywords. The h-index accounts for the productivity and impact of individual or group research based on the most cited articles. A quantity of 4,480 citations was counted related to the keyword used. Regarding relevance, the selection of articles demonstrated a 38 h-index score (Figure 3).

Figure 3 - Web of Science citations report croptamine terms.



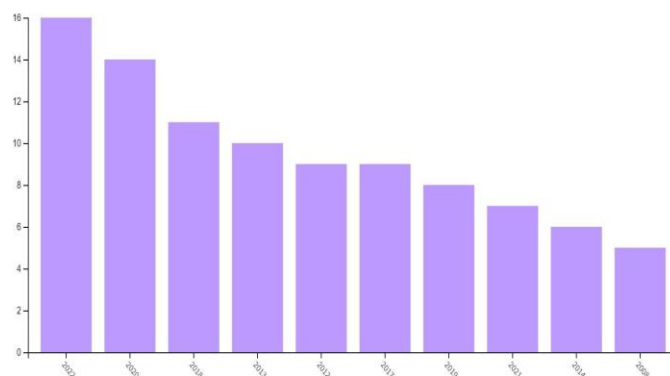
Analyzing the WOS data categories studied in (Figure 4), it was found that the areas of Toxicology (71), Pharmacology (66), and Molecular Biology (48) are among the most prominent publications, representing 40,34%, 37,50%, and 27,28%, respectively (Figure 4).

Figure 4 - Data category statement.



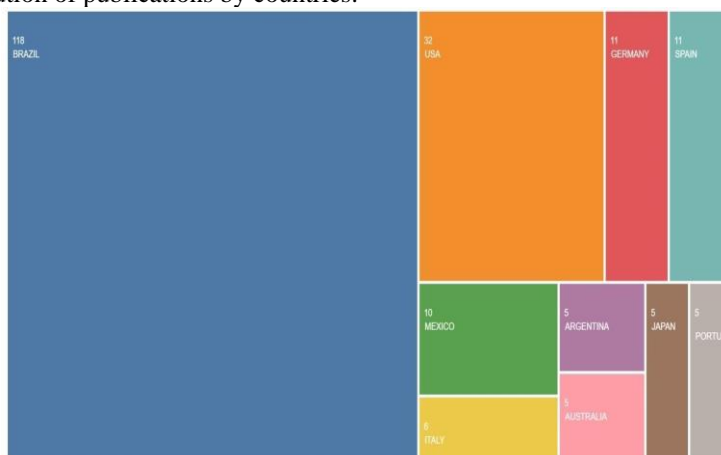
Regarding annual publications, we identified 16 publications in 2022 (9%), 14 publications in 2020 (7,96%), and 11 publications in 2018 (6,25%) (Figure 5).

**Figure 5 -** Distribution of publications by year.



Twenty-five countries and regions had studies and publications, among which Brazil leads with 118 articles published (67,05%), followed by the USA with 32 publications (18,18%) and Germany (6,25%), and Spain with 11 articles each (6,25%). Among South American countries, Argentina stands out with five publications (2,84%). Australia, Japan, and Portugal were countries that also stood out, each with five publications (Figure 6).

**Figure 6 -** Distribution of publications by countries.



Among the funding agencies, we can highlight the National Council for Scientific and Technological Development (CNPq), with 48 publications (27,27%), the Research Support Foundation of the State of São Paulo (FAPESP), with 41 publications (23,3%), Coordination for the Improvement of Higher Education Personnel (CAPES) with a total of 31 publications (17,61%). American funding agencies: National Institutes of Health (NIH) and United States Department of Health and Human Services, with seven publications each, and the Spanish Government with six publications (Figure 7).

**Figure 7-** Distribution of publications by financing agencies.



With the use of VOS Viewer 1.6.16 software, an analysis of the visualization network was carried out. Thus, data from the bibliometric network were grouped through maps from different perspectives. Therefore, data from co-authorship networks by country and author cocitation networks were selected, bearing in mind that the other data were detailed in the WOS database survey.

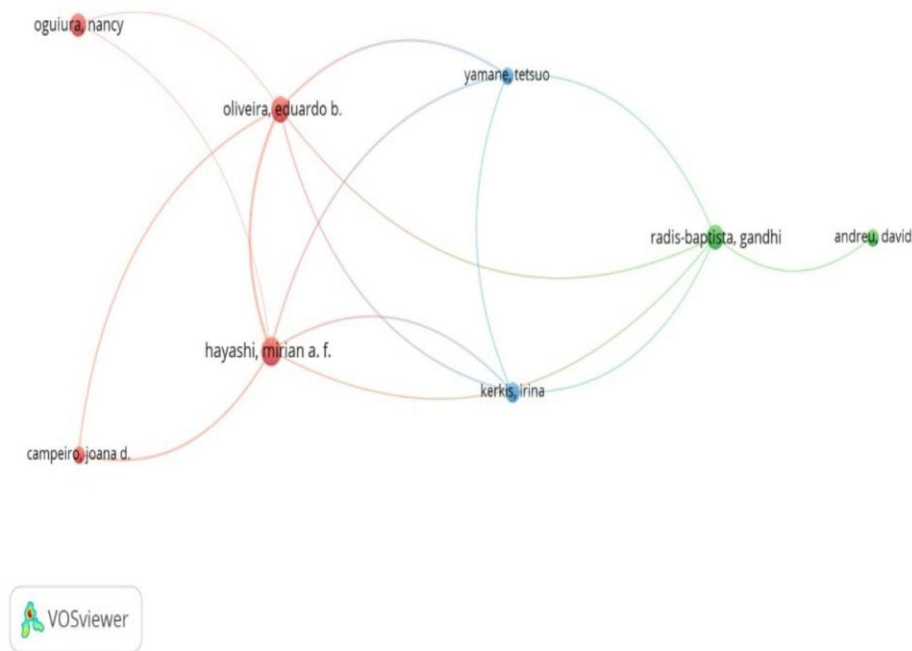
The relationship between researchers is essential for scientific research so that scientific knowledge can reach academia and the social environment. In this way, a network of publications is formed, establishing connections conducive to disseminating discoveries and scientific studies. Thus, this tool's cocitation analysis allows for identifying this network of relationships and how it is established between countries, authors, and institutions.

The representation of this network occurs in the form of circles and branches. The larger the circle, the greater the representativeness of the indicator through the generated sample; as for the ramifications, the more they appear, the more connections and relationships it presents.

Observing the clusters generated by co-authorship, 3 clusters highlighted in green, red, and blue were identified in the sample. The cluster shown in red includes four authors: Joana D. Campeiro, Mirian A. F. Hayashi, Oguiura Nancy, and Eduardo Brandt Oliveira. In green, cluster number 2 shows Gandhi Radis-Baptista and David Andreu, and finally, the cluster in blue highlights Irina Kerkis and Tetsuo Yamane (Figure 8).



**Figure 8 - Cocitation networks.**

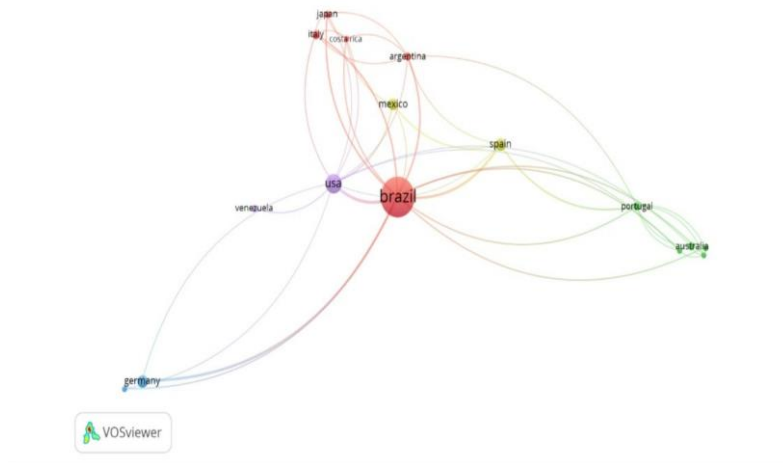


In the same way, it is possible to identify, through the generated clusters, the interrelationships formed by the co-authorships by countries, making it possible to identify the progress of research published in the most different academic areas, in addition to visualizing the nucleus to which they belong, and the collaboration maintained between the authors. By observing the co-authorship clusters generated by countries, it is possible to identify how authors, institutions, and countries relate and collaborate, identifying and mapping the most relevant characteristics in common.

The co-authorship of authors from different countries makes it possible to verify the growth of studies published in different academic areas, identifying the nucleus to which they belong and measuring the level of collaboration between the authors, and the advent of new themes.

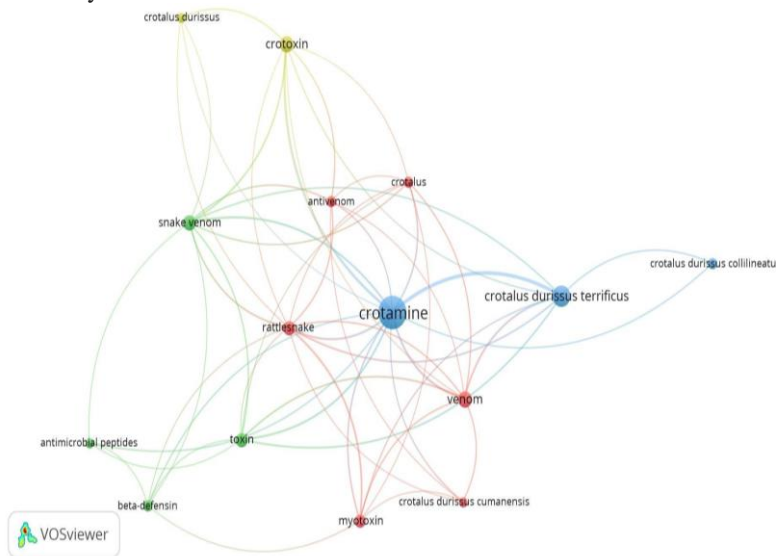
For this research, samples of co-authors with three published documents and three citations per country were considered in the co-authorship relationship between countries. Sixteen countries were found that met the established criteria. Brazil stands out with the most published works: the United States and Germany (Figure 9).

**Figure 9** - Co-authorship networks by countries.



The network map generated by VOS Viewer through the records obtained from the WOS database using the keywords used by the authors measured 4 clusters where the terms "Crotalus durissus terrificus", "venom" and "toxin" are highlighted in colors blue, red, and green, respectively (Figure 10).

**Figure 10** - Authors' keyword networks.

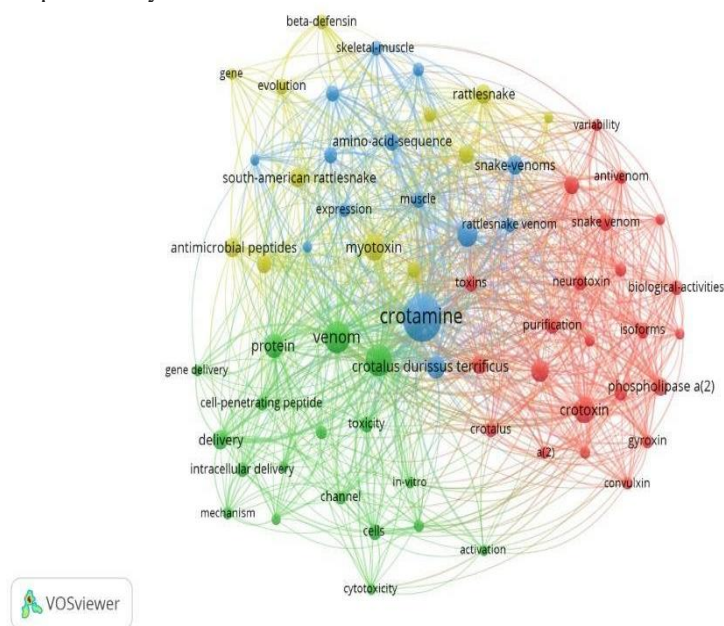


The map highlights "crotamine" as the central concept of all established relationships. Among the other concepts that have a greater connection with the others, "Crotalus durissus terrificus" and "toxin" stand out. The cluster in red contains six terms, namely: "antivenom", "Crotalus", "Crotalus durissus cumanensis", "myotoxin", "rattlesnake" and "venom", this being the most significant cluster. In green, the cluster

brought the following items: "antimicrobial peptides", "beta-defensin", "snake venom", "toxin". In the representation of the blue-colored cluster: "Crotalus durissus collineatu", "Crotalus durissus terrificus" and "crotamine". In the yellow color, only two terms appeared: "Crotalus durissus" and "crotoxin".

Another possibility that this bibliometric analysis tool offers is the visualization of the network formed by all the keywords of the imported documents, such as title and abstract (Figure 11). In this type of analysis, the strengths of the connections generated in the network still point to the term "crotamine" as the most prominent. This means that with the term in the title of all documents, the CTA is the central theme of the articles. Regarding the formation of clusters, the map presented four groupings. The largest, consisting of 23 terms, is represented in red with "crotoxin" highlighted. The second cluster, highlighted in green, has 18 items, with the term "venom" being more representative. The third cluster identified by the blue color appears with 14 items, revealing the term "crotamine" as a highlight. In yellow, the fourth and last cluster highlights the term "myotoxin" and comprises 12 items.

**Figure 11** - Map of all keywords.



The use of bibliometric methods in this research around the term "crotamine" sought to answer the question: what is the perspective of scientific production on CTA myotoxin, according to bibliometric criteria? The investigation of the arrangement of articles over the years made it possible to verify when the first document on the subject

was published. In addition, an advance in publications can be seen, with the year 2022 being the one with the highest number of records and the last five years (2017 to 2021) corresponding to 27,84% of the entire sample. Regarding the authors, the analysis showed the most productive names and their interrelationships in knowledge transfer.

In the analyzes referring to the data and funding agencies category, it was possible to know the area's most relevant groups and institutions. Moreover, finally, analyzing the keywords, the theme researched showed the main concepts related to the central theme, corroborating the already known versatility of this toxin. In the years that comprised this study, the number of documents on CTA increased considerably, reaching its peak in 2022. Its ability to act as a cell penetration peptide was studied [17-22] (PONNAPPAN; CHUGH, 2017; RODRIGUES et al., 2013; MALUF et al., 2016; CHEN et al., 2012; CAMPEIRO et al., 2019; JOSHI et al., 2022) and duly reviewed by several authors (RÁDIS-BAPTISTA, 2021; KERKIS et al., 2014; KERKIS et al., 2017; REISSMANN; FILATOVA, 2021), in addition to its properties: antitumor [CAMPEIRO et al., 2018; PEREIRA et al., 2011) including its synthetic compound (DE CARVALHO PORTA et al., 2020), antibacterial (OGUIURA et al., 2011), antifungal (DAL MAS et al., 2016), in addition to its use in association with drugs in the treatment of leishmaniasis (VALENTIM-SILVA et al., 2022) and others.

The distribution of scientific productions per year shows a growing number of researchers enthusiastic about research on this myotoxin. On the other hand, there are still gaps, and more related studies may continue to explore this issue. Furthermore, allied to the development of the social economy, more attention is being focused on health (SUNG et al., 2021). Diseases such as cancer (which continues to be the highest incidence and the second cause of death worldwide) and infectious diseases such as leishmaniasis still suffer from outdated, resistant, high-toxicity therapies, severe side effects, and high cost. It is reasonable that joint efforts by researchers result in even greater production in this type of research.

Regarding the results of the analyzes related to authors, countries, and funding institutions, the data proved to be polarized in a single country, assuming greater interest in researchers from that region, as it is the native geographic area of the object of study. There is, therefore, the need to establish connections between Brazilian authors and other countries, such as the USA and Germany, which also showed interest in studying CTA. International collaboration is paramount for knowledge exchange and subsidies from

interested development institutions. The relevance of studies involving this myotoxin must be considered, considering that its chemical, pharmacological and biotechnological properties can bring solutions in this area.

Furthermore, the urgent nature of new therapeutic agents for treating diseases that suffer from ineffective treatments makes studies of this category important. In the analysis of the keywords, "toxin", "venom" and "protein" were the most common in the studies. The analysis of the frequency of words showed how these terms are involved, mainly in the study of toxicity, delivery, cell penetration peptide, and intracellular delivery, indicating the priority of research with this theme. The nod in the perspectives of studying the CTA in the field of in vitro fertilization, malaria, and fungus is worth mentioning.

Although this is the first bibliometric study on CTA, potential limitations should be highlighted: the mention of CTA only in the documents in their titles, abstracts, or keywords were exported from the database. Therefore, relevant documents may need to be included, resulting in an incomplete analysis. However, a search was also carried out in the patent bank. Another obstacle is that the WOS Core Collection platform was chosen as the exclusive database, given its conformation with the selected visual analysis software and, inevitably. However, this platform is one of the most recognized databases, and some studies may still need to be recovered. It should be paid attention to the evolution of scientific publications, as bibliometric studies can offer direction for a relatively short period since citation numbers and keywords can be changed frequently. Other bibliometric analyzes also mentioned this gap.

## **CONCLUSION**

This study is the first bibliometric article focusing on CTA myotoxin. Through visual analysis or clusters, detailed information from numerous publications can be captured in a more intuitive way. The last ten years have seen growth in research, and given the versatility of the CTA, the number of documents will continue to increase. Brazil leads regarding authors and funding agencies regarding the number of publications, followed timidly by the USA and Germany. Undoubtedly, new ideas and exciting studies will inspire other researchers in similar scientific areas to delve deeper into solutions to this problem. However, this polypeptide's valuable characteristics must still be developed and deepened. Overall, this research draws on data from published research papers and provides a visual reference for further studies involving the CTA peptide.

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