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MEDICINAL SPECIES OF THE GENUS CROTON (EUPHORBIACEAE): A WORLDWIDE VIEW ON THE DYNAMICS AND EVOLUTION OF SCIENTIFIC PRODUCTION

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ABSTRACT

Objective: the present study aimed to gather scientific information on a worldwide level about publications on the Croton genus, with the identification of the main medicinal species, their bioactive compounds and medicinal uses, using information published in journals and different and complementary references in the area of applied botany, supporting research with species of this genus.

Theoretical framework: Croton genus is one of the largest of the Euphorbiaceae family and contains approximately 1,300 species, many of which used in traditional medicine for treating stomach disease, abscess, inflammation, and malaria. The use of bibliometric surveys has been developing for years, grouping information and aiding decision-making in all areas, especially human health and environmental sciences.

Method: Web of Science platform was used to obtain data, we compiled the documents found considering various information. For the analysis, the Bibliometrix package from the RStudio software was used, as well as the IRAMUTEQ software.

Results and conclusion: mapping of scientific production recorded 64 species in the 354 papers found, in investigation or confirmation of medicinal potential. The main bioactivities examined were the anti-inflammatory, antimicrobial, antioxidant, antinociceptive, anticancer, and antimalaria actions.

Research implications: Brazil stood out in the following aspects: number of publications, collaborations, and affiliations with active research about the genus, which can be attributed to the genus' degree of endemism in this country.

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Originality/value: this unprecedented study constitutes relevant support for future research involving the bioactive potential of new Croton species and even other plants of popular medicinal use.

Keywords: Ethnobotany, Mapping of Scientific Production, Medicinal Potential, Medicinal Use, Bibliometrics.

ESPÉCIES MEDICINAIS DO GÊNERO CROTON (EUPHORBIACEAE): UMA VISÃO MUNDIAL SOBRE A DINÂMICA E EVOLUÇÃO DA PRODUÇÃO CIENTÍFICA

RESUMO

Objetivo: o presente estudo teve como objetivo reunir informações científicas em nível mundial sobre publicações sobre o gênero Croton, com a identificação das principais espécies medicinais, seus compostos bioativos e usos medicinais, utilizando informações publicadas em periódicos e referências diferentes e complementares na área. de botânica aplicada, apoiando pesquisas com espécies deste gênero.

Referencial teórico: o gênero Croton é um dos maiores da família Euphorbiaceae e contém aproximadamente 1.300 espécies, muitas das quais utilizadas na medicina tradicional para tratamento de doenças estomacais, abscessos, inflamações e malária. A utilização de pesquisas bibliométricas vem se desenvolvendo há anos, agrupando informações e auxiliando a tomada de decisões em todas as áreas, especialmente nas ciências humanas e ambientais.

Método: utilizou-se a plataforma Web of Science para obtenção dos dados, compilamos os documentos encontrados considerando diversas informações. Para a análise foi utilizado o pacote Bibliometrix do software RStudio, bem como o software IRAMUTEQ.

Resultados e conclusão: o mapeamento da produção científica registrou 64 espécies nos 354 artigos encontrados, em investigação ou confirmação de potencial medicinal. As principais bioatividades examinadas foram as ações antiinflamatória, antimicrobiana, antioxidante, antinociceptiva, anticancerígena e antimalária.

Implicações de pesquisa: o Brasil se destacou nos seguintes aspectos: número de publicações, colaborações e afiliações com pesquisas ativas sobre o gênero, o que pode ser atribuído ao grau de endemismo do gênero neste país.

Originalidade/valor: este estudo inédito constitui suporte relevante para futuras pesquisas envolvendo o potencial bioativo de novas espécies de Croton e até mesmo de outras plantas de uso medicinal popular.

Palavras-chave: Etnobotânica, Mapeamento da Produção Científica, Potencial Medicinal, Uso Medicinal, Bibliometria.

1 INTRODUCTION

Since ancient times, plants have been used in the treatment of diverse diseases and are still used in medicine until today. The World Health Organization estimates that 85% of the world population uses medicinal plants, their extracts, and their active ingredients as an alternative treatment for diseases and dysfunctions (WHO, 2003). According to Salmeron-Manzano et al. (2020), ten percent of all vascular plants are used as medicinal plants and it is estimated that there exist between 350,000 and 500,000 species with medicinal potential. For Garlet & Irgang (2001), the carrying out of studies in the area of ethnobotany should occupy a prominent position, bearing in mind the relationship between the human being and the plants, as well as the form of use of the resources. With this, the origin of the scientific interest in the

popular knowledge about medicinal plants of popular use is in the confirmation of knowledge about analyses and tests that confirms scientifically such cultural learning.

Euphorbiaceae is the sixth largest angiosperm family, holding approximately 300 genera and 8,000 species (Govaerts et al., 2000). The *Croton* L. genus is one of the largest of the family, containing approximately 1,300 species distributed predominantly in the tropical regions, but also native in subtropical and temperate areas in the northern hemisphere (Berry et al., 2005). Its diversity is concentrated mainly in Brazil, Antilles, Mexico, Madagascar, and Ethiopia. Many species of the *Croton* genus are used in traditional medicine for treating stomach disease, abscess, inflammation, and malaria, especially in regions of Africa, southern Asia, and South America (Burger & Huft, 1995). The bioactivity with medicinal potential of the *Croton* genus plants is directly linked to their secondary metabolites, while flavonoids, terpenes, and alkaloids are the main classes of compounds found. Thus, this is a genus of paramount importance and has already been considered this way around the world (Xinan & Yimin, 2004; Heywood et al., 2007; Salatino et al., 2007; Sena-Filho et al., 2008).

The bibliometric survey, or bibliometrics, differs from the literature review because it requires a series of methodological steps and standardized techniques, capable of reproduction, based on the grouping and combination of information, aiming at systematically supporting decision-making. This methodology is based on evidence and on the movement of scientific research at world level and of the need for validating obtained results, from other studies relative to given issues of interest. The use of systematic bibliographic reviews showing the state of the art has been developing for years in several areas gathering information or even replacing what is known as primary research, aiding decision-making in all areas, and in particular, in human health and forest science (Song & Zhao, 2013; Uribe-Tori et al., 2019; Polinko & Coupland, 2021; Baena-Pedroza et al., 2021; Gómez-Domínguez et al., 2022; Tlili et al., 2022). In the specific case of the *Croton* genus, there is still a lack of bibliometric information measuring the contribution of the scientific knowledge derived from the publications.

In a recent paper, Prado et al. (2022) present a bibliometric analysis of the *Croton* genus as a literature review grounding laboratory test, also described in the same paper, for antioxidant evaluation of *Croton antisyphiliticus* Mart. (Euphorbiaceae). In that review, the authors restricted the searches to a specific bioactivity "antioxidant"; as observed in their methodology, the keywords and search operators were "Croton", "antioxidant activity", and "Euphorbiaceae". A total of 326 papers were identified in the initial search, however, of these, only 89 met the standards desired by the authors and were considered for the documentary corpus composition. In the data analysis, eight parameters were considered (areas of knowledge; areas of research; types of documents; analysis of time; publication year; editors; countries and regions; consolidated organizations). The formation of graphs showed a timeline from 1995 to 2020; a network of correlation of keywords; and a correlation network between periodicals about antioxidant activity and *Croton* genus species.

There is a great lack of comprehensive studies about the diverse medicinal applications, beyond antioxidant activity, of the *Croton* genus, in spite of this new document found, especially with keywords involving more variables such as anti-inflammatory, antimicrobial, antioxidant, antinociceptive, anti-cancer, antimalaria activity and others fundamental for a corpus that comprises the broad use potential of the genus species, including a timeline that seeks since the first document, found in the Web of Science database, which dates from 1963.

The present study aimed to carry out a bibliometric study about the *Croton* genus species medicinal use, gathering scientific information at world level about studies published in journals and the combination of different and complementary references in the great area of applied botany, with the identification of the main species, their bioactive compounds and

medicinal uses, generating graphics using the RStudio software, with the Bibliometrix package, and IRAMUTEQ.

2 MATERIALS AND METHODS

The work presented was carried out following the steps described in the Graphical Methodology (Figure 1).

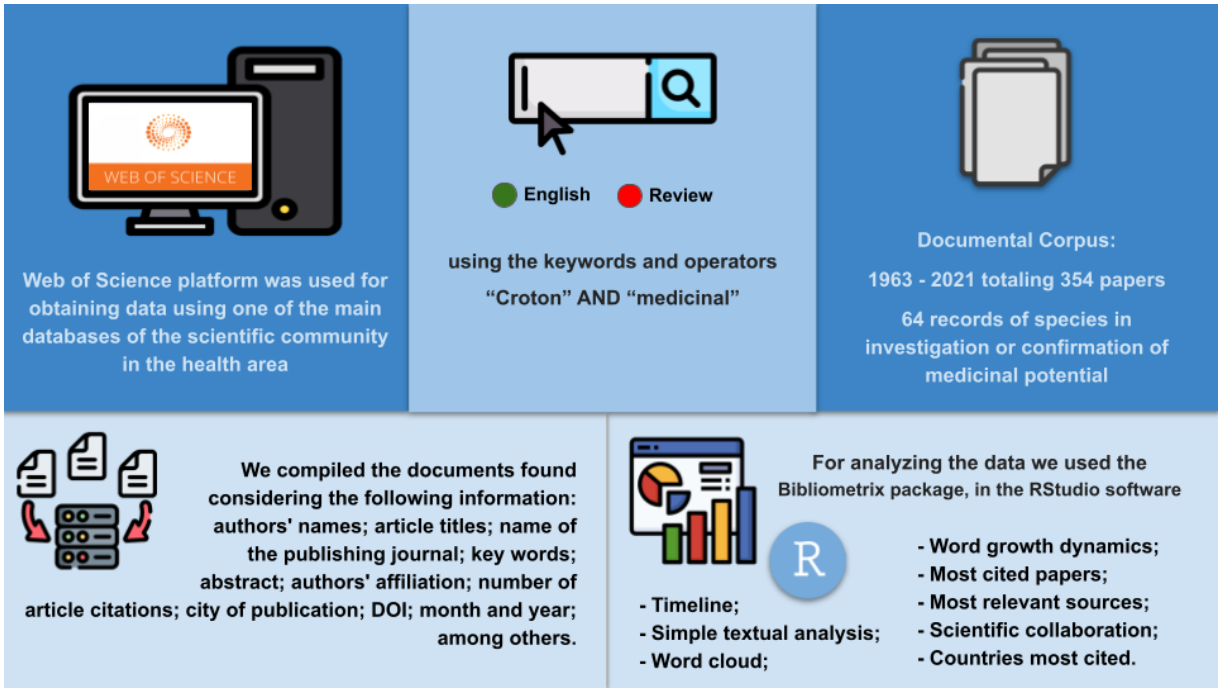

Figure 1- Graphical Methodology.
Source: Prepared by the authors (2023)

2.1 Platform and Data Collection

The Web of Science platform was used for obtaining data using one of the main databases of the scientific community in the health area. To orient the searches, reading of introductory papers was done, and from the first semester of 2022, we began the search for papers available in the platform using the keywords and operators "Croton" AND "medicinal". Documents from the first publication (1963) until records from 2021 were considered. After that, language filters (accepting only the documents in English because of the ease of communication and distribution around the world) and filters of exclusion of review papers were applied, aiming for the creation of a most homogeneous possible documental corpus.

2.2 Documentary Corpus

We compiled the documents found considering the following information: authors' names (reduced and full); titles of the papers; name of the publication journal; keywords; abstract; authors' affiliation; ORCIDs; development agency (when existing); number of citations of the paper; city of publication; ISSN and DOI; month and year; areas; and Pudmed Id.

2.3 Data Processing and Analysis

For analyzing the data, we used the Bibliometrix package in the RStudio software, which is a complete package for the scientific mapping workflow, providing every tool to carry out a complete bibliometric analysis (Aria & Cuccurullo, 2017). The package works from the download of data of different bibliographic databases and from the upload of data, while it is possible to carry out varied analyses with graphs of its own and dynamic, by means of methodology described by Aria & Cuccurullo (2017). Furthermore, we used the IRAMUTEQ software, where simple textual analyses were generated by the "statistics" function from the quantification of the frequency (number of repetitions) of each term (Xavier et al., 2019). Eight graphs were generated for discussion by Bibliometrix: "Timeline", viewing the publication dynamics around the world, from the first publication on the platform to the last one recorded in the last year, 2021; "Cloud Word", which highlights the most frequent terms in keywords, abstracts, and titles; "Word Growth Dynamics", which follows the most frequent terms according to consecutive years; "Most Cited Papers", observing the relevance of themes; "Most Relevant Sources", journals around the world most notable for publication in the area; "Scientific Collaboration" and "Most Cited Countries", understanding connections around the world; and by IRAMUTEQ: "Simple Textual Analysis", viewing in different periods the high and low frequency of terms in titles, keywords, and abstracts.

3 RESULTS AND DISCUSSION

The paper sought to use comprehensive search operators, in order to obtain a wide search for overall medicinal activity. In total, 15 parameters were considered for analyses. The total of papers within the prerequisites was 354 (Supporting Information). After the survey, it was possible to trace a broad profile of publications about the *Croton* genus for the period of approximately 68 years.

3.1 Timeline

The temporal panorama of publications about the *Croton* genus is contained in the graph of annual scientific production (Figure 2). The first paper was published in 1963, followed by other two publications in 1971 and 1989, therefore a rather reduced number of publications occurred until the end of the 1990s. At the beginning of the twentieth century there was a substantial increase in annual publications, maintaining at the very least ten papers by year.

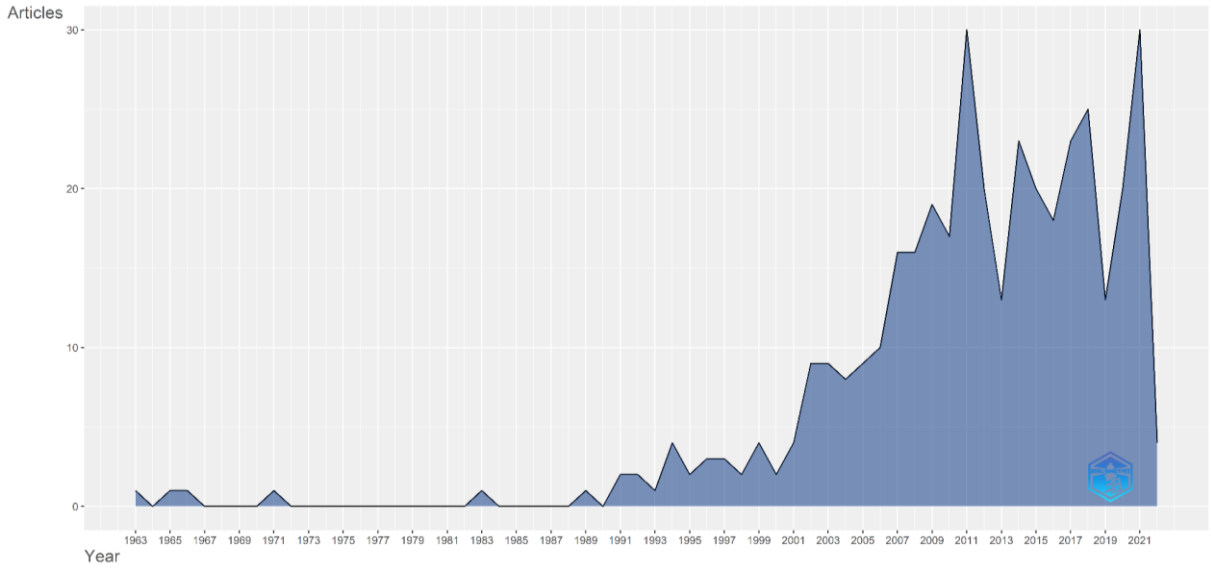

Figure 2- Annual scientific production from the first publication in 1963 to the last recorded in 2021.
Source: Prepared by the authors (2023)

The first publication (Vanduuren et al., 1963) is a short communication and addresses the isolation of some specific molecules, with purgative action of the crystalline, a bioactive fraction of the *Croton tiyliuin* L. A. seeds essential oil. The second publication (Arroyo & Holcomb, 1965) describes the complete separation of isolation of the molecule described as main C-3 compound, carried out through the combination of methods of extraction, column chromatography, countercurrent distribution, and thick-layer chromatography. The third one (Hecker et al., 1966) brings some alterations in the structural model proposed of the molecules isolated by Arroyo & Holcomb (1965). The publications are indexed in Journal of Medicinal Chemistry and available in digital form.

3.1.1 Simple textual analysis, by period

Simple textual frequency (f) graphs (Figure 3) were generated via the IRAMUTEQ software for titles and keywords in three periods: from 1963 to 1999 (Figure 2A), from 2000 to 2010 (Figure 2B), and between 2011 and 2021 (Figure 2C). It is possible to observe that in the three periods there are few terms with high frequency and several terms with low frequency. In the period from 2011 to 2021 we see a high quantity of terms repeated twice, probably because they are repeated in titles and keywords (Figure 2C).

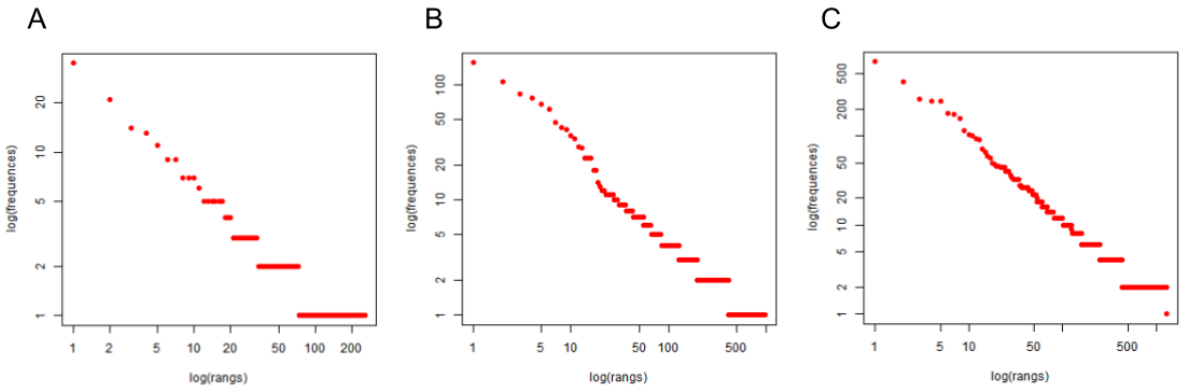

Figure 3- Simple textual frequency between terms from titles and keywords. A) period from 1963 to 1999; B) period from 2000 to 2010; C) period from 2011 to 2021.
Source: Prepared by the authors (2023)

Until 1999 there is a record of 29 published papers, within the patterns described. The main area was Chemistry, followed by Pharmacy and Pharmacology, Medicine, Molecular Biology, and Plant Science. The main *Croton* genus species cited were *C. cajucara* Benth., *C. megalocarpus* Hutch., *C. nepetifolius* Baill., *C. tiglium* L., *C. zambesicus* Müll. Arg., and *C. zehntneri* Pax & K. Hoffm.

Between the years 2000 and 2010 one has an increase in publications: 128 papers recorded, characterized especially within the areas of Pharmacy and Pharmacology, Medicinal Chemistry, Plant Science, Integrative and Complementary Medicine, and in the areas of Biochemistry and Molecular Biology, Food Science and Technologies, and General Chemistry. The most cited species among the publications were as follows: *C. cajucara*, *C. celtidifolius* Baill., *C. flavens* L., *C. floribundus* Spreng., *C. gratissimus* Burch., *C. lechleri* Müll. Arg., *C. lobatus* L., *C. macrostachyus* Hochst. ex Delile, *C. menthodorus* Benth., *C. montevidensis* Spreng., *C. nepetifolius*, *C. niveus* Jacq., *C. pullei* Lanj., *C. roxburghii* N.P. Balakr., *C. schiedeanus* Schltdl., *C. stellatopilosus* H. Ohba, *C. tiglium*, *C. tonkinensis* Gagnep., *C. xalapensis* Kunth, *C. zambesicus*, and *C. zehntneri*. The most studied compounds are the groups of alkaloids, coumarins, steroids, flavonoids, cardioactive glycosides, lignans, essential oils, saponins, and triterpenes.

From 2011 until the end of 2021 there is a record of 277 publications, which showed a rather varied species profile: *C. adipatus* Kunth, *C. antisyphiliticus* Mart., *C. bonplandianus* Baill., *C. cajucara*, *C. campestris* A. St.-Hil., *C. cascarilloides* Raeusch., *C. caudatus* Geiseler, *C. ceanothifolius* Baill., *C. celtidifolius*, *C. collinus* Kunth, *C. conduplicatus* Kunth, *C. cordiifolius* Baill., *C. crassifolius* Geiseler, *C. dichogamus* Pax, *C. elegans* Kunth, *C. euryphyllus* W.W. Sm., *C. flavens*, *C. floribundus*, *C. gratissimus*, *C. grewioides* Baill., *C. heliotropiifolius* Kunth, *C. lachnocarpus* Benth., *C. laui* Merr. & F.P. Metcalf, *C. lechleri*, *C. lobatus*, *C. macrobothrys* Baill., *C. macrostachyus*, *C. matourensis* Aubl., *C. megalobotrys* Müll. Arg., *C. megalocarpoides* Friis & M.G. Gilbert, *C. membranaceus* Müll. Arg., *C. menthodorus*, *C. montevidensis*, *C. nepetifolius*, *C. niveus*, *C. oblongifolius* Sieber ex Spreng., *C. penduliflorus* Hutch., *C. piauhiensis* Müll. Arg., *C. pullei*, *C. reflexifolius* Kunth, *C. rhamnifolioides* Pax & K. Hoffm., *C. roxburghii*, *C. schiedeanus*, *C. sonderianus* Müll. Arg., *C. sphaerogynus* Baill., *C. stellatopilosus*, *C. sylvaticus* Hochst., *C. tetradenius* Baill., *C. thurifer* Kunth, *C. tiglium*, *C. tonkinensis*, *C. urucurana* Baill., *C. xalapensis*, *C. yunnanensis* W.W. Sm., *C. zambesicus*, and *C. zehntneri*. Essential oil was the most cited compound (f>50), followed by "diterpenes" (f=22), "flavonoids" (f=6), and "alkaloids" (f=4). "Anti-inflammatory" activity stands out among the analyzed texts, then we see "potential" indicating

investigative research, and next “antimicrobial” and “antioxidant”, “cytotoxic”, “antibacterial”, “antisyphilis”, “antinociceptive”, “anticancer”, and other terms with f<10.

3.2 Recurrent terms

In Figure 4, we present the word cloud, which shows an overall view of the simple textual frequency (f) of titles and abstracts. Of the ten most cited words, which constitute the cloud’s central axis, we have in first “leaves”, with f=27, followed by the words “extracts”, f=26; “extract”, f=25; “constituents”, f=24; “essential oil”, f=23; “antioxidant”, f=19; and “antimicrobial activity”, “chemical-composition” and “in-vitro”, all with f=18. This gives us a clear view that the main compounds extracted from *Croton* species are obtained from their leaves, which shows that the use of these species can be explored without the plant’s destruction.

Figure 4- Word cloud generated by the authors from texts from title, keywords, and abstract, in the Bibliometrix platform.
Source: Prepared by the authors (2023)

Figure 5 shows the growth dynamics for terms related to bioactivity. The most cited words in titles, paragraphs, and keywords arise from the 1990s and have a more perceptible increase in the first years of 2000. Following the same path as the word cloud, the most cited term was “antimicrobial activity”, followed by “antioxidant”, “chemical composition”, “constituents”, “essential oil”, “extract” and “extracts”, “in vitro”, “leaves”, and, not surprising, “medicinal plants”, showing the scientific interest and potential medicinal use of compounds present in the *Croton* genus.

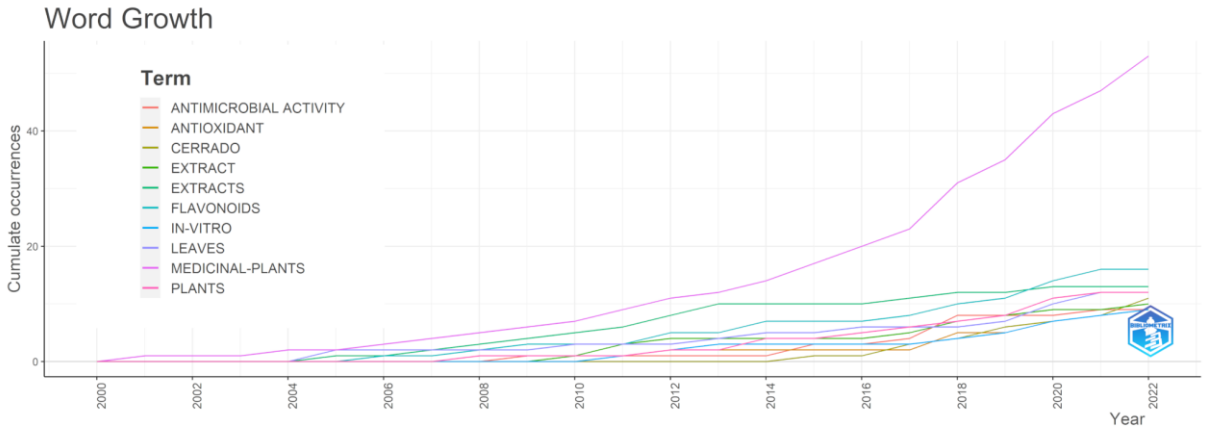

Figure 5- Growth dynamics of cited words.
Source: Prepared by the authors (2023)

3.3 Documents

We present in Figure 6 the most cited studies' description, along with first author and journal of publication. The most cited paper, Conforti et al. (2008), titled "In vivo anti-inflammatory and in vitro antioxidant activities of Mediterranean dietary plants", was indexed in Journal of Ethnopharmacology. The second most cited is from Phillipson (2001), published in Phytochemistry and titled "Phytochemistry and medicinal plants". In third place, Giday et al. (2007), published in Journal of Ethnopharmacology, which sought to compile and analyze knowledge about the use of medicinal plants (among them *Croton macrostachyus*) for treating or preventing human disease in territories of traditional peoples in the northwest of Ethiopia.

In fourth place, we have Lall and Meyer (1999), which tested *in vitro* the antibacterial action of *Croton pseudopulchellus* and other South-African plants, toward strains of *Mycobacterium tuberculosis* resistant and sensitive to drugs, published in Journal of Ethnopharmacology. And in fifth place we have Sosa et al. (2002), which carried out a screening of the anti-inflammatory activity of plants from Central America, against edema induced by high doses of essential oil of a *Croton* genus species, also published in Journal of Ethnopharmacology.

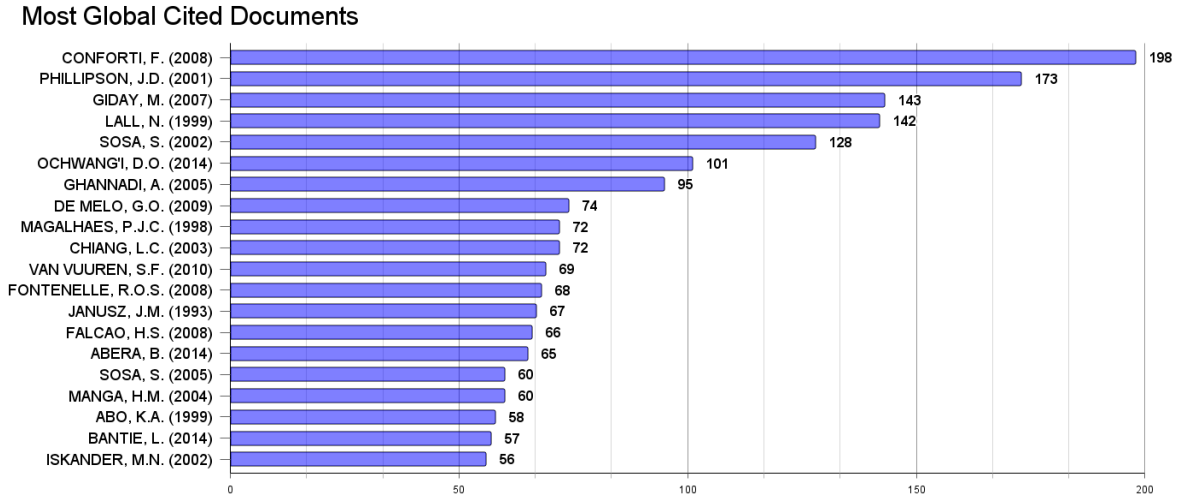

Figure 6- Most cited documents worldwide.
Source: Prepared by the authors (2023)

Furthermore, we have related studies, such as research about medicinal plants used in treating cancer (Ochwang'i et al., 2014); investigation of the analgesic and anti-inflammatory effect of seeds (Ghannadi et al., 2005); antiviral activity (Chiang et al., 2003); intestinal myorelaxant and antispasmodic effects of *Croton nepetaefolius* essential oil (Magalhães et al., 1998); investigation of the antimicrobial activity of traditional plants from southern Africa in treating sexually transmissible infections (van Vuuren & Naidoo, 2010); assessment of the antifungal activity of the essential oils of *Croton* genus species present in the Brazilian Caatinga (Fontenelle et al., 2008); antiulcer activity of American plants (Falcão et al. 2008); investigation of the antimicrobial potential of *Spondias mombin*, *Croton zambesicus*, and *Zygotritonia crocea* (Abo et al., 1999); ethnobotanical studies of plants used in traditional medicine by the Oromo people, southwest of Ethiopia (Abera, 2014); and assessment of the antimalarial activity *in vivo* of the extract of *Croton macrostachyus* Hochst. (Bantie et al., 2014).

In Figure 7 are presented the most relevant sources of research, where it is possible to predict what source would be the most relevant. Once by the data generated in collecting papers, eight of the 20 most relevant papers were published in Journal of Ethnopharmacology, this journal is considered the most relevant source in the studies about medicinal compounds of the *Croton* genus species. The journal is dedicated to the exchange of information on and understanding of the use of plants, fungi, animals, microorganisms and minerals, and their biological and pharmacological effects on the basis of principles established by international conventions.

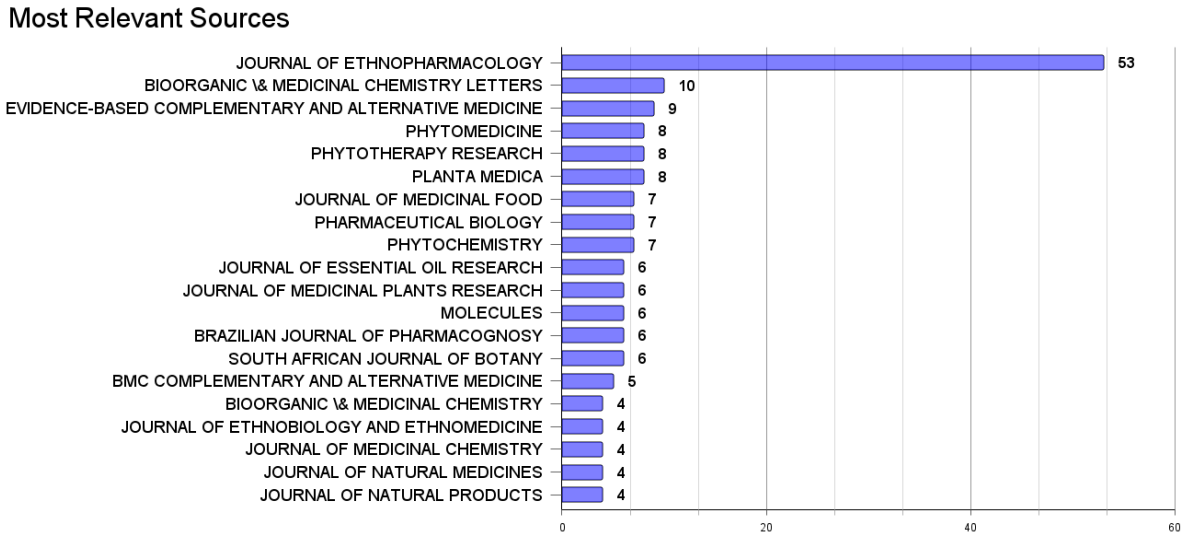

Figure 7- Most relevant sources on a global level found in the study.
Source: Prepared by the authors (2023)

3.4 Scientific Production by Country and Collaborations

In Figures 8 and 9, it is possible to see, respectively, the scientific production and collaboration by country, and the most cited countries around the world about the *Croton* genus species medicinal use. Results demonstrate in an evident way that Brazil is ahead both in absolute number of publications and in collaborations' quality.

The analyses of publication by country show Brazil as main world scientific producer and collaborator, establishing collaborations with Argentine (1), Bangladesh (1), Colombia (1), Cuba (2), Equator (1), Iran (1), Italy (6), Paraguay (3), Portugal (4), Thailand (1), United Kingdom (1), and USA (4).

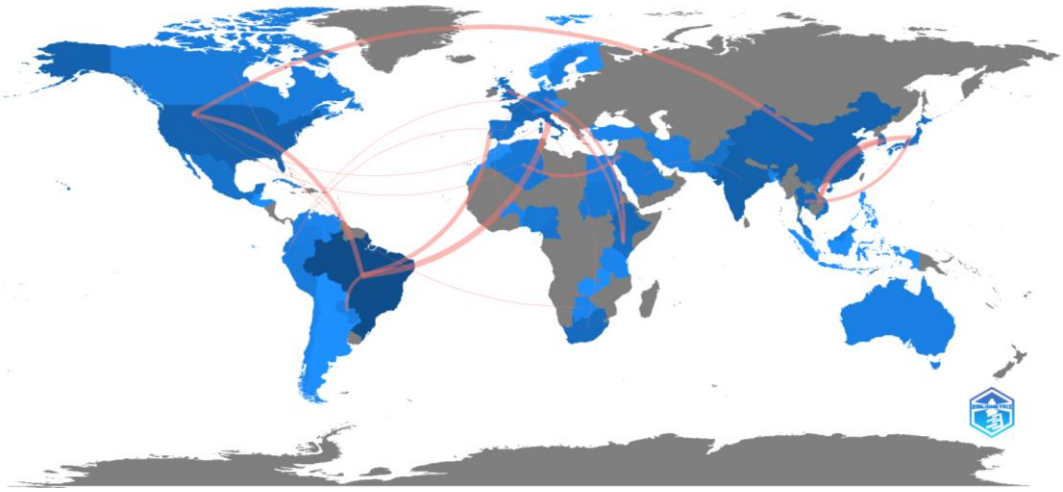

Figure 8- Scientific production and collaboration by country around the world.
Source: Prepared by the authors (2023)

Complementing the graph of world production, Brazil is also the most cited country (Figure 9), with frequency higher than 1,700 citations. Although Italy has been the country with most collaborations with Brazil, the country had less than ⅓ of the frequency of Brazilian citations (little more than 500). Such a highlight occurs because of the number of Brazilian publications, collaborations, and affiliations with active research about the genus, as well as due to the degree of endemism of the genus in the country (Heywood et al. 2007).

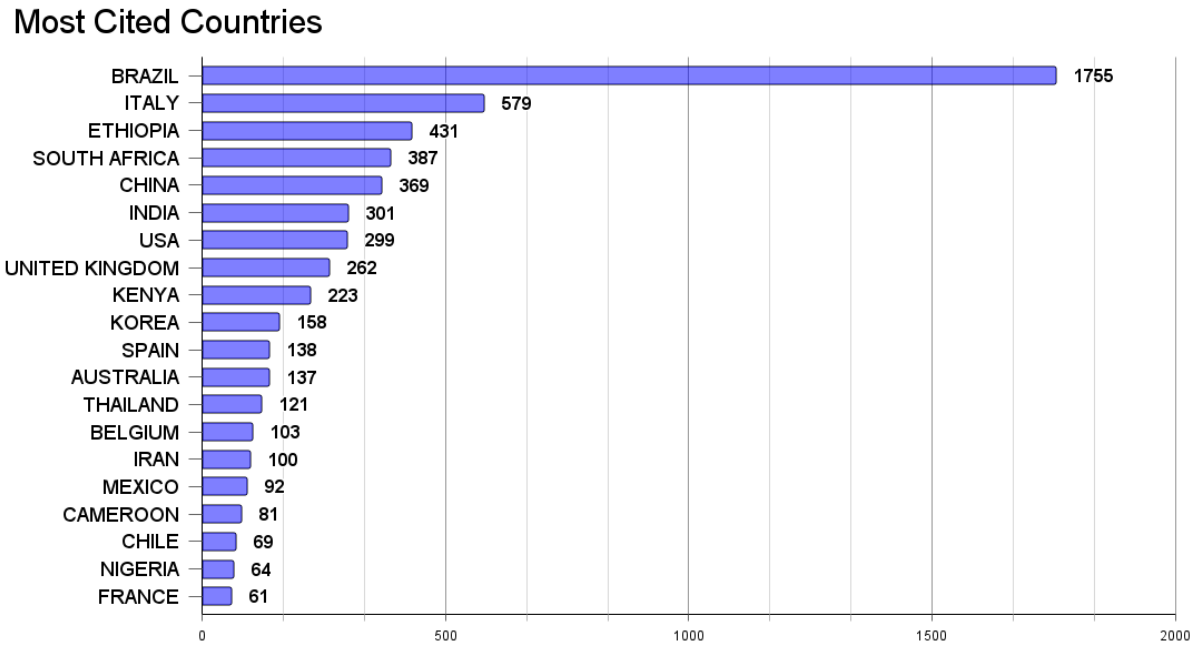

Figure 9- Countries most cited around the world.
Source: Prepared by the authors (2023)

4 CONCLUSIONS

The mapping of scientific production from 354 papers analyzed of the Web of Science platform, obtained the result of 64 records of species in investigation or confirmation of medicinal potential. This datum corresponds to 5% of the already described species, which demonstrates the importance of the genus and its species.

The most examined medicinal uses were the anti-inflammatory, antimicrobial, antioxidant, cytotoxic, antibacterial, anti-syphilis, antinociceptive, anticancer, antimalarial, antiestrogenic, antispasmodic, antiplasmodial, analgesic, antiallergic, and antimycotic actions.

Among the main isolated compounds with bioactivity, the alkaloids, coumarins, steroids, flavonoids, cardioactive glycosides, lignans, essential oils, saponins, diterpenes, and triterpenes classes stand out, showing the wide spectrum of use of the species in the medicinal field.

It is worth stressing that in addition to demonstrating the state of the art of the world scientific production about studies with medicinal compounds of *Croton* species, we highlight Brazil as the leader in scientific production through its number of publications, collaborations, affiliations with active research, and high degree of endemism of the genus in the country, constituting a relevant contribution to future research that involves bioactive potential of new *Croton* species and even other plants of popular medicinal use.

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