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Bibliometric Analysis as a Tool for the Study of the *Croton* Genus and Antioxidant Evaluation of *Croton antisyphiliticus* Mart (Euphorbiaceae)

Análise Bibliométrica como Ferramenta para o Estudo do gênero Croton e Avaliação Antioxidante de Croton antisyphiliticus Mart (Euphorbiaceae)

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The targeted investigation on the biological activity of the species of the genus *Croton* using bibliometric analysis as a tool for the search allows for a systematic review of the literature, as well as the assessment of current quantitative research trends on the subject. In this research, the bibliometry of *Croton* species based on analysis of the antioxidant activity available and published in Web of Science and PubMed databases were carried out. In view of the lack of data regarding the antioxidant activity for *C. antisyphiliticus* Mart., the ethanolic extracts as well as fractions from the roots, stem and leaves were evaluated against the DPPH radical scavenging activity. The results showed high DPPH antioxidant activity for the leaves (IC_{50} 35.53 μg mL^{-1}), stem (IC_{50} 47.14 μg mL^{-1}) and fraction from stem (IC_{50} 15.7 μg mL^{-1}). Thus, we can infer that bibliometric analysis could be considered an important tool to guide research not only on the antioxidant activity of *C. antisyphiliticus,* but of other species as well. Furthermore, the reviewed information about the antioxidant potential of the genus *Croton*, findings from this research on the *C. antisyphiliticus* species are of significant value which contributes to the chemotaxonomic characterization of this species.

Keywords: Antioxidant potential; bibliometric analysis; *Croton antisyphiliticus*; phytochemistry

1. Introduction

Bibliometric analysis is a study that combines a set of techniques applied to statistical and mathematical methods to analyze data associated with a given knowledge. The study follows a certain sampling logic to obtain information from a bibliographic survey, as well as conclusions about a search.[1] Bibliometric methods have several applications as the evaluation of a research institution, a systematic literature review, the identification of trends and knowledge growth in an area, as well as the emergence of new themes and the selection of outstanding journals; the prediction of publishing trends; the analysis of the productivity of authors, organizations, countries and their correlations; citation and co-citation processes and the comparison of common study between universities. Moreover, in bibliometric analysis, citation analysis allows the identification and description of several patterns in the production of scientific knowledge and their impacts, institutional origin of the most influential authors in a particular field of research, and the most used document type.[2]

Bibliometric analysis is regarded as an important tool that could be used to guide research on a certain subject. It performs analysis on the reviewed literature using a scientific method that tends to reduce or minimize bias. This systematic review technique is characterized by the following steps: a) sample definition; b) descriptive statistics; c) network analysis; and d) content analysis. Although bibliometrics is widely used in several areas, in chemistry there is still inadequate information, particularly with regard to some plant species. This study intends to utilize this technique to explore the biological activity of the *Croton* genus.

Croton is the second largest genus of Euphorbiaceae family which comprises about 1300 species distributed in different climatic regions of the world.[3,4] Out of 350 endemic species of these regions, Brazil has around 252 of these species,[5,6] in which the *Croton* species are highly valued due to their marked biological activities. These include cytotoxic, antifungal, antibacterial and anti-inflammatory activities.[3] Besides microbial activity, the antioxidant activity of *Croton* species extracts such as *C. celtidifolius*,[7] *C. cajucara*,[8] *C. lechleri*,[9] *C. sparsiflorus*

Morong,[10] *C. gratissimus* Burch[11] and *C. zambesicus* Müll. Arg[11] have also been reported. The antioxidant activity has been attributed to the phenolic acids, flavonoids (isoflavones, catechins, quercetins) and tannnins [3,8,11] which are present in several medicinal plants. These compounds possess the ability to scavenge free radicals, as well as others reactive oxygen and nitrogen species, and to prevent or reduce serious health problems related to oxidative damage, such as premature ageing, neurodegeneration and cancer.[12] Unfortunately, the biological activities of certain species within the genus *Croton* are either unknown or the existing literature is scarce. Thus, bibliometric analysis explored in this research aided the verification of data scarcity/absence about the antioxidant potential of *C. antisyphiliticus*.

C. antisyphiliticus species popularly known as "pé-de-perdiz" ("partridge foot"— lit. translation into English) is found in the Cerrado of Brazil, a tropical savanna ecoregion, and is widely used in folk medicine for its therapeutic properties.[13] The species ethnobotanical study revealed its use in the treatment of syphilis, rheumatism, ulcer wounds and urinary tract inflammations.[13, 14] In view of the aforementioned bioactivities, the current study was designed to explore the antioxidant activity of the *C. antisyphiliticus* species that has not been previously reported with particular reference to the use of bibliometric analysis.

2. Material and Methods

2.1. Bibliometrics analysis

A systematic bibliometric study was carried out to collect information on the antioxidant activity of the *Croton* genus. The databases used in this study were the Web of Science and PubMed. The keywords "*Croton*", "*antioxidant activity*" and "*Euphorbiaceae*" were surveyed. At this stage, we correlated the scientific articles obtained through bibliometric analysis.

The next step consisted of descriptive statistics, in which the main characteristics of the surveyed topic were observed - still using the databases as a support tool and analyzing the parameters within a given theme, time or field. Descriptive statistics is important for identifying the most relevant article for the bibliographic survey and the contribution of this article. At this stage, 326 results were obtained from the keywords searched. This enabled an overview of the bibliographic survey, followed by a descriptive analysis of topic at hand.

In order to decrease the universe of research and thereby obtain a greater sensitivity of the data the definition of the surveyed topic was carried out based on the analysis of the parameters: the areas of knowledge that presented the highest number of publications, the types of documents (including only scientific articles published in English), temporal analysis of the productivity of publications, years of publications (1995-2020), editors with more publications on the topic, countries and regions where more research projects are carried out on the topic and consolidated organizations that have greater relevance and are most cited in this topic.

Subsequently, an analysis of the networks in which the relations between the documents found and the selected articles were observed was performed, in order to have general notions of content and to analyze the main references of the sample. The VOSviewer software was used to create correlation networks for certain themes which had as focus, in this case, the antioxidant activity of the *Croton* genus. Thus, correlation networks of journals and keywords were built.

Finally, the content analysis was carried out systematically to deepen the discussion of the content. The most prominent and cited references were analyzed herein, in addition to examining the most relevant connections.

Interestingly, the information obtained via the use of bibliometric analysis showed no report about antioxidant activity of *C. antisyphiliticus*. In view of this, therefore, the antioxidant potential of this species was evaluated.

2.2. Plant material

Access to the genetic heritage was registered at the National System of Genetic Resource Management and Associated Traditional Knowledge (SisGen) under code number A11AE20. Roots, stem and leaves of *C. antisyphiliticus* were collected in the city of Catalão, Goiás State, Brazil, and authenticated by Dr. Núbia A. M. P. Gomides, Biotechnology Institute, Federal University of Catalão. A voucher specimen (UFG-27.850) has been deposited at the same institution

2.3. Extraction

The air-dried roots (151 g), stem (54 g) and leaves (71 g) were pulverized in a knife mill, extracted at room temperature with ethanol (Merck, Darmstadt, Germany) (3 × 9 L, 9 days each), filtered and concentrated to yield the ethanolic extracts of roots (EER) (28.0 g, 18.5%), stem (EES) (4.4 g, 8.1%) and leaves (EEL) (8.7 g, 12.2%). The solid-phase extraction (SPE) technique was used to fractionate the EER, EES and EEL extracts. Stationary phase cartridges composed of LC-18 Supelclean™ (Merck, Darmstadt, Germany) were coupled to a Supelco Visiprep™ SPE vacuum manifold (Supelco, St. Louis, MO, USA). To activate each cartridge, 18 mL of methanol (Merck, Darmstadt, Germany) were initially applied and subsequently 6 mL of ultrapure H_2O were used for conditioning. Then, 100 mg of each extract solubilized in 6 mL of CH_3OH was applied. The first elution consisted of 6 mL ultrapure H_2O and 6 mL CH_3OH, resulting in the subfractions EER1 (33.0 mg), EES1 (42.0 mg) and EEL1 (40.7 mg). The second elution consisted of 2.4 mL ultrapure H_2O and 9.6 mL CH_3OH, leading to the subfractions EER2

(29.6 mg), EES2 (24.0 mg) and EEL2 (17.8 mg). The third and last elution consisted of 12 mL of CH_3OH, which resulted in EER3 (33.2 mg), EES3 (14.0 mg) and EEL3 (12.8 mg) subfractions.

2.4. Quantification of total phenolic content

The total phenolic content was measured using the Folin-Ciocalteu colorimetric method as described by Sousa *et al*.[15] with modifications by Nunes *et al*.[16] Standard solutions (10.0, 20.0, 40.0, 60.0, and 80.0 μg mL^{-1}) of gallic acid (Sigma-Aldrich, St. Louis, MO, USA) were prepared in CH_3OH and used to construct a calibration curve (R^2 = 0,981). The total phenolic content was expressed as milligrams of gallic acid equivalents (mg GAE g^{-1}).

2.5. Quantification of flavonoid content

The total flavonoids content was determined using the method described by Woisky & Salatino[17] with modifications by Nunes *et al*.[16] The quercetin (Sigma-Aldrich, St. Louis, MO, USA) standard compound solutions (5.0, 10.0, 20.0, 30.0, and 40.0 μg mL^{-1}) were prepared in CH_3OH and used to construct a calibration curve (R^2 = 0,992). The flavonoid content was expressed as milligrams of quercetin equivalents (mg QE g^{-1}).

2.6. Quantification of condensed tannins

The total proanthocyanidins content was determined by the sulphuric vanillin method described by Morais *et al*.[18] with modifications by Nunes *et al*.[16] The catechin (Sigma-Aldrich, St. Louis, MO, USA) standard compound solutions (5.0, 10.0, 15.0, 20.0, 25.0, and 30.0 μg mL^{-1}) were prepared in CH_3OH and used to construct a calibration curve (R^2 = 0,978). The proanthocyanidins content was expressed as milligrams of catechin equivalents (mg CE g^{-1}).

2.7. DPPH radical-scavenging activity

The measurement of the 2,2-diphenyl-1-picrylhydrazyl radical (DPPH - Sigma-Aldrich, St. Louis, MO, USA) scavenging activity was performed according to a modified method of Brand-Williams *et al*.[19] The samples EER, EES, EEL, EER1, EER2, EER3, EES1, EES2, EES3, EEL1, EEL2, EEL3 were solubilized in CH_3OH (1 mg mL^{-1}) and diluted to different concentrations ranging from 500 μg mL^{-1} to 7.81 μg mL^{-1}. The test was performed adding 2800 μL of methanolic DPPH solution (40 μg mL^{-1}) with 200 μL of sample. The mixture was incubated for 40 min in the dark, and the absorbance of unreacted DPPH was used as the control. The DPPH scavenging activity was determined spectrophotometrically at 517 nm. The gallic acid was used as standard compound, and the percentage DPPH scavenging effect was calculated using the following equation (Equation 1).

$$\%\ \text{DPPH scavenging} = [(Abs_{517nm}(\text{control}) - Abs_{517nm}(\text{sample}))/Abs_{517nm}(\text{control})] \times 100 \quad (1)$$

where, Abs_{517nm}(control) is the absorbance of the control and Abs_{517nm} (sample) is the absorbance of the reaction mixture containing the test sample.

The IC_{50} value which is the sample concentration required to inhibit 50% of the free radical DPPH was calculated from the regression equation for the sample concentration and percentage inhibition.

2.8. Statistical analysis

Measurements were performed in quintuplicate and expressed as mean ± standard deviation (SD). Data were assessed for normal distribution using the Ryan-Joiner test while statistical significance of the samples was carried out using one-way analyses of variance (ANOVA) with multiple *post hoc* comparison tests (Tukey test). The Minitab 18.0 software was used for analyses considering the accepted statistical significance level for the *p*-value was less than 0.05.

3. Results and Discussion

3.1. Bibliometric study

The survey was conducted rigorously and consistently. Each analytic parameter was specific (i.e what is to be measured/analyzed; what results is to be obtained and whether it addresses the set objectives). With these sets of specific parameters, it was possible to verify the scientific productivity, each year, in relation to the *Croton* genus. In addition, it allowed for the quantitative analysis of *Croton* species's antioxidant potentials and other biological activities already covered/reported in scientific articles. It also probes the destination of a research i.e., to specific or multidisciplinary journals.

A total of 326 articles were identified in the search. Systematic review of the literature made it possible to survey the antioxidant potential of many species of the *Croton* genus, such as *C. celtidifolius*,[7] *C. cajucara*,[8] *C. lechleri,*[9] *C. sparsiflorus* Morong,[10] *C. gratissimus* Burch[11] and *C. zambesicus* Müll. Arg[11] and others. From this, eight parameters (areas of knowledge; areas of research; types of documents; analysis of time; years of publications; editors; countries and regions; consolidated organizations) were selected in order to obtain and correlate the utmost amount of information in an organized way. Thus, the parameters identified as relevant for this study were drawned from 89 articles.

The analysis of descriptive statistics shown the number of scientific articles published per year and the productivity of the researched theme over the years. It was observed, when evaluating as parameters the analysis of time and years of publications, that 2018 was both the peak year of

articles published on the subject and the peak productivity of the researched theme over the years (Figure 1).

This was mentioned at the beginning of studies on the antioxidant potential of *Croton* species by Jones *et al*.[20] Since then, there has been a significant increase in the number of published papers on the antioxidant activity of species of the *Croton* genus and thereby increasing productivity on this topic. Publications related to antioxidant activity of *Croton* species revealed a drop in the number of articles. The trend reached its peak in 2018 and fell again in 2019. Thus, it can be concluded that although there was no consistency in the list of articles published per year, there was a significant number of publications related to the subject and the *Croton* genus, therefore demonstrating the visibility and relevance of this research.

The correlation obtained from the databases used was elaborated based on the keywords defined for this study (i.e., *Croton*; antioxidant activity; Euphorbiaceae), as well as by keywords cited by the authors of selected publications. It was observed that correlation from network between the keywords of the selected articles, antioxidant activity and Euphorbiaceae (Figure 2) highlighted the biological potential regarding the antioxidant capacity of the *Croton* genus. Utilizing this technique, it was possible to identify in literature and from the network, species of the genus with notorious activity, such as *C. cajucara*, *C. lecheri*, *C. conduplicatus* and *C. celtidifolius*.

Regarding the secondary metabolites responsible for the antioxidant activity for species of the *Croton* genus, the correlation network in Figure 2 shows the presence of flavonoids, which are aromatic compounds belonging to the class of phenolic compounds. Flavonoids are metabolites widely described in the Euphorbiaceae family. Reports of antioxidant activity for species *C. celtidifolius,*[7] *C.* cajucara,[8] *C. lechleri*,[9] *C. urucurana*[21] and others are linked to the presence of compounds like quercetin, naringenin, kaempferol and myricitrin.[7-11,21]

Finally, the most published journals which present the greatest relevance on the subject investigated. The correlation network presented in Figure 3 showed that the Journal of Ethnopharmacology has the largest number of publications related to the antioxidant potential of species of *Croton* genus.

It was also noticed that the journals Phytochemistry, Planta Medica and Phytomedicine presented a considerable number of publications, which directly cross-referenced with the Journal of Ethnopharmacology through direct citations of the papers published in this journal. Similarly, it was observed that the journals with lower number of publications on the antioxidant potential of species of *Croton* genus demonstrate the visibility, relevance and impact factor of the papers published in the Journal of Ethnopharmacology. These publications are cited as references, directly and indirectly, by other journals.

3.2. Evaluation of the antioxidant activity of *C. antisyphiliticus*

The systematic literature review carried out using bibliometric analysis showed a strong contribution of phenolic compounds, especially flavonoids and tannins (proanthocyanidins), to the antioxidant activity of species such as *C. cajucara*, *C. urucurana*, *C. celtidifolius*, *C. zambesicus*, *C. lechleri*, and *C. Brasiliensis*.[7-11] Considering that phenolic compounds are essential in plant metabolism hence, they are biosynthesized in high contents. In this study, the quantification of total phenolic content, as well as the evaluation of the presence of flavonoids and tannins, it was necessary to evaluate the antioxidant potential of *C. antisyphiliticus* extracts, which are shown in Table 1.

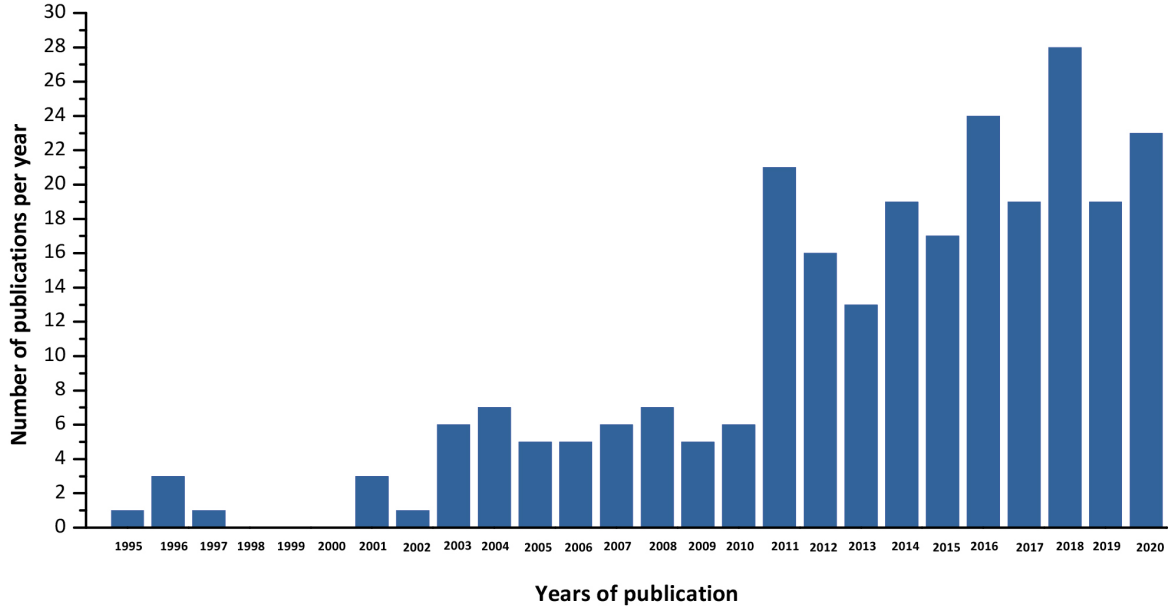

Figure 1. Relationship between amount article published per year regarding the antioxidant activity of species of the genus *Croton*

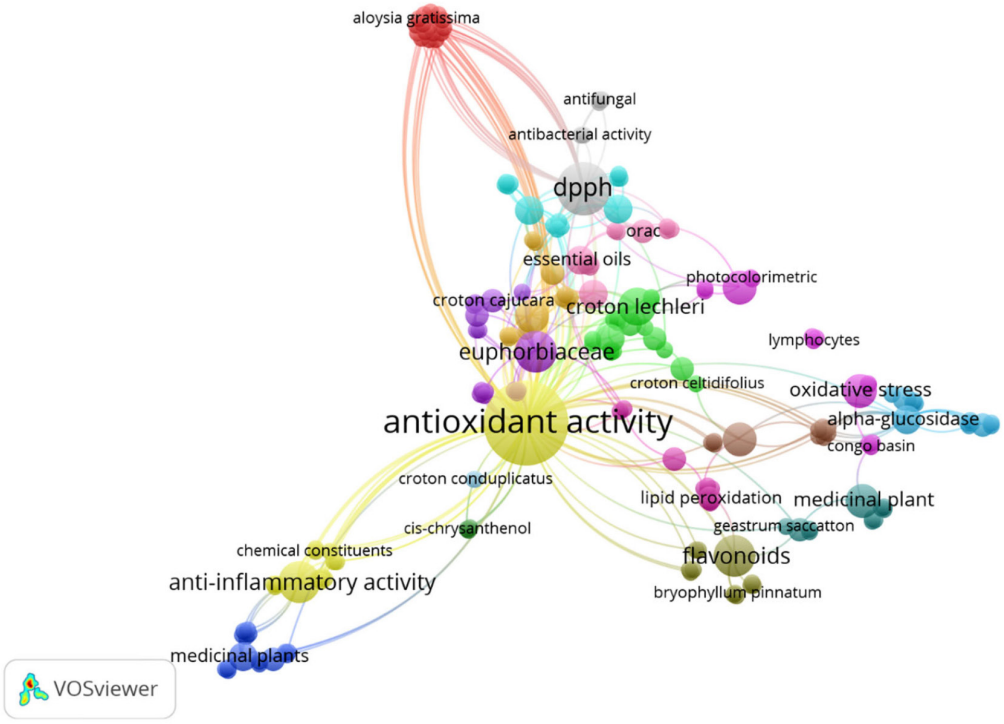

Figure 2. Keywords correlation network in every bibliographic search

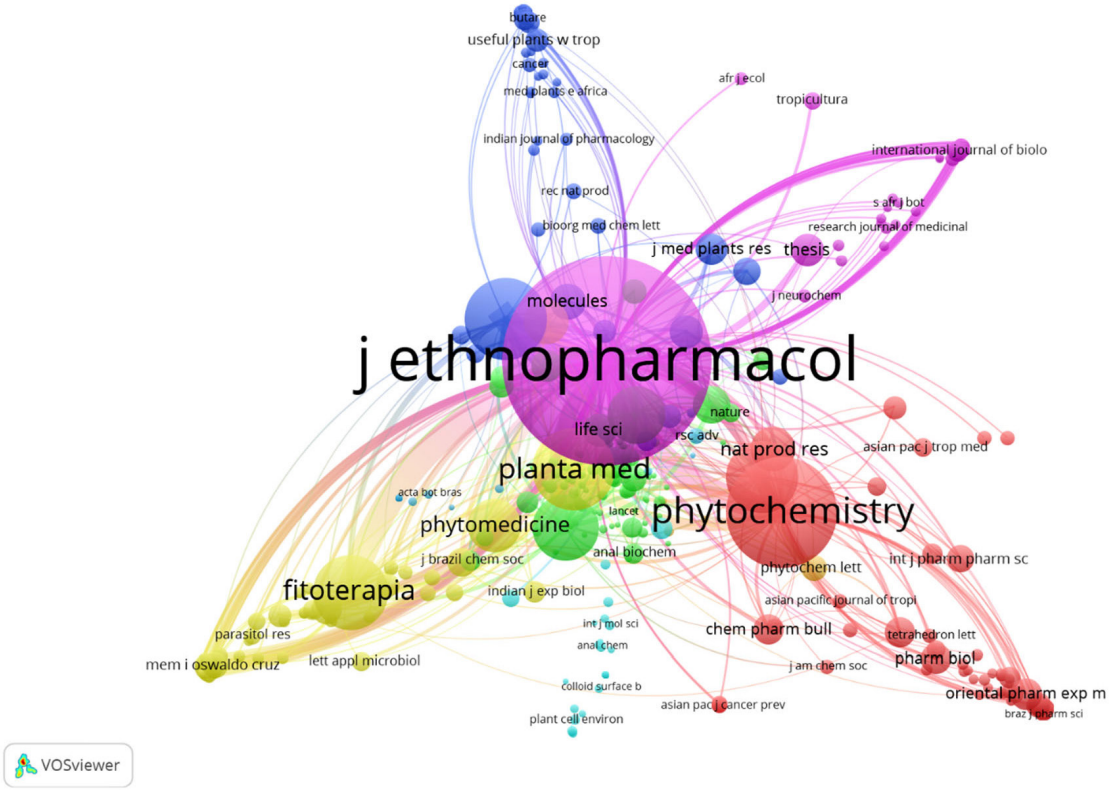

Figure 3. Correlation network between journals about antioxidant activity and species of the *Croton* genus

Among the extracts evaluated, EES (996.0 ± 0.00 mg g^{-1}) and EEL (995.0 ± 0.00 mg g^{-1}) samples presented high levels of phenolic compounds, which were not differentiated by ANOVA ($p < 0.05$), exhibiting higher values when compared to other species of the *Croton* genus. The EEL sample had the highest content of flavonoids (187.20 ± 0.00 mg g^{-1}) and tannins (186.0 ± 0.00 mg g^{-1}), differently from the other extracts ($p > 0.05$).

Table 1. Total phenolic content (expressed in mg GAE g^{-1} sample), flavonoids content (expressed in mg QE g^{-1} sample) and tannins content (expressed in mg CE g^{-1} sample) in *Croton antisyphiliticus* extracts

Extracts	Total phenolic content	Flavonoids content	Tannins Content
Ethanolic extract of roots (EER)	887.00 ± 0.07a	171.19 ± 0.04c	166.95 ± 0.11f
Ethanolic extract of stem (EES)	996.00 ± 0.09b	181.30 ± 0.02d	180.95 ± 0.04g
Ethanolic extract of leaves (EEL)	995.00 ± 0.03b	187.20 ± 0.05e	186.50 ± 0.06g

Values (means of five replicates) followed by different letters are significant different at $p < 0.05$.

Table 2. DPPH Scavenging activity test on extracts and fractions of *Croton antisyphiliticus* (expressed as inhibitory concentration in μg mL^{-1})

Roots		Stem		Leaves	
Extract	IC_{50}	Extract	IC_{50}	Extract	IC_{50}
EER	468.93 ± 0.07a	EES	47.14 ± 0.03b	EEL	35.53 ± 0.06b
Fractions		Fractions		Fractions	
EER1	260.90 ± 0.04c	EES1	11.73 ± 0.04d	EEL1	112.55 ± 0.05e
EER2	> 1000f	EES2	666.40 ± 0.09g	EEL2	213.20 ± 0.02h
EER3	> 1000f	EES3	> 1000f	EEL3	546.23 ± 0.06i
gallic acid			32.17 ± 0.06b		

Values (means of five replicates) followed by different letters are significant different at $p < 0.05$.

The evaluation of the antioxidant potential of *C. antisyphilliticus* was based on the mechanism of action of phenolic compounds to combat oxidative stress through the deactivation of free radicals via electron transfer, or hydrogen atoms, which form stable molecules.[15,21] The IC_{50} values obtained for extracts and fractions of *C. antisyphiliticus* are shown in Table 2. Among the samples evaluated, three presented high sequestrating capacity of DPPH radicals. The EES1 fraction (11.73 ± 0.04 μg mL^{-1}) showed the best value of antioxidant activity, differing statistically from other samples ($p > 0.05$), and exhibited inhibition levels of DPPH lower than the gallic acid standard compound (32.17 ± 0.06 μg mL^{-1}). The antioxidant activities of EES (47.14 ± 0.03 μg mL^{-1}) and EEL (35.53 ± 0.06 μg mL^{-1}) extracts were noteworthy, although the findings did not present any statistical distinctions ($p < 0.05$) in relation to the standard. The concentration-response, given by IC_{50} value, estimates the concentration required of sample of *C. antisyphiliticus* to reduce the initial concentration of DPPH by 50%. Thus, we can infer that composition rich in phenolic compounds, such as flavonoids and tannins, as well as the synergy between these compounds, may have contributed to the high antioxidant activity of EES1, EES and EEL.

The IC_{50} values obtained, together with the evaluation by ANOVA (Table 2), indicated the hypothesis related to the different levels of free radical inhibition ($p > 0.05$) by the samples. From the analysis of multiple comparisons, using the Tukey test, the high antioxidant potential of EES and EEL extracts was confirmed. This was evident from the similarities obtained using paired comparison between the IC_{50} values of *C. antisyphilliticus* extracts and the values observed for the standard compound gallic acid. Among the evaluated fractions, only the EES1 sample exhibited a remarkable antioxidant potential, in which the statistical treatment indicated difference of $p > 0.05$. In this report, this is the first time the IC_{50} value of a sample EES1 was lower and exceeded the antioxidant capacity of the standard compound.

The paired comparison analysis using the Tukey test aims to inform which samples are different within the sample set of a reference, based on the evaluation of the minimum significant difference between all possible pairs, as well as determining the confidence intervals.[23,24] Thus, through of the Tukey test, it could be verified that EES, EEL and EES1 presented the best values of antioxidant activity among the samples evaluated for *C. antisyphilliticus*.

4. Conclusions

The bibliometric study on the *Croton* genus described in this work provided information about its antioxidant potential. In this sense, knowledge about the chemical and biological potential of the species *C. antisyphilliticus* has been amplified. The IC_{50} values obtained from samples of *C. antisyphilliticus* confirmed its promising antioxidant potential. The high antioxidant activity of the ethanolic extracts from the stem and leaves was also emphasized, as well as the enriched EES1 fraction. Finally, this study would like to suggest further research on identification and elucidation of bioactive compounds in other parts of the species *C. antisyphilliticus* as well as in other species within the *Croton* genus. This would be aimed at the discovery of drug lead compounds as well as bioproducts with cosmeceutical applications.

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