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Croton sp.: a review about Popular Uses, Biological Activities and Chemical Composition

Croton sp.: uma revisão sobre Usos Populares, Atividades Biológicas e Composição Química

Croton sp.: una revisión sobre Usos Populares, Atividades Biológicas y Composição Química

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Abstract
The genus *Croton*, belonging to the Euphorbiaceae family, is a plant with shrubby characteristics, with the ability to regrow in times of rain, develops wildly, especially in deforestation areas, being reported mainly in the Caatinga and Forest region. One of the main characteristics of this genus is that several species are rich in chemical constituents of importance for medicine. In this way, this review of the literature, has an objective that findings regarding the biological activities and chemical composition of *Croton* species. This study is a literature review, carried out in the following databases: SciELO, BVS, MEDLINE, LILACS, PubMed and ScienceDirect, with a time frame between 1997 and 2020. The articles studied have shown different activities for *Croton* species, such as anti-inflammatory, antihypertensive, antifungal, antimicrobial, antidiabetic, antioxidant, antinociceptive and anti-tumor. Regarding toxicological aspects, the findings suggest caution in the use of *Croton* species, as some are toxic. While, regarding the chemical composition, in most species the presence of several secondary metabolites is observed, such as alkaloids, terpenoids, flavonoids and other phenolic compounds. Therefore, the results described in this article suggest that the therapeutic application of *Croton* species is supported by the literature, however we point out that caution is required in the use of *Croton* species, some present due to toxicity.
Keywords: *Croton* sp; *Croton blancheantius*; Biological activities; Chemical composition; Toxicology.

Resumo
O gênero *Croton*, pertencente à família Euphorbiaceae, é uma planta com características arbustivas, com capacidade de rebrota em épocas de chuva, desenvolve-se de forma selvagem, principalmente em áreas de desmatamento, sendo relatada principalmente na Caatinga e na região da Floresta. Uma das principais características desse gênero é que várias espécies são ricas em constituintes químicos de importância para a medicina. Desta forma, esta revisão da literatura, tem como objetivo obter descobertas a respeito das atividades biológicas e composição química das espécies de *Croton*. Este estudo é uma revisão da literatura, realizada nas seguintes bases de dados: SciELO, BVS, MEDLINE, LILACS, PubMed e ScienceDirect, com período compreendido entre 1997 e 2020. Os artigos estudados mostraram diferentes atividades para espécies de *Croton*, como anti-inflamatório, anti-hipertensivo, antifúngico, antimicrobiano, antidiabético, antioxidante, antinociceptivo e antitumoral. Em relação aos aspectos toxicológicos, os achados sugerem cautela no uso de espécies de *Croton*, pois algumas são tóxicas. Já quanto à composição química, na maioria das espécies observa-se a presença de diversos metabólitos secundários, como alcaloides, terpenóides, flavonoides e outros compostos fenólicos. Portanto, os resultados descritos neste artigo sugerem que a aplicação terapêutica de espécies de *Croton* é suportada pela literatura, porém ressaltamos que é necessário cautela no uso de espécies de *Croton*, devido à toxicidade.
Palavras-chave: *Croton* sp; *Croton blancheantius*; Atividades biológicas; Composição química; Toxicologia.

Resumen
El género *Croton*, perteneciente a la familia Euphorbiaceae, es una planta de características arbustivas, con capacidad de rebrote en épocas de lluvia, se desarrolla salvajemente, especialmente en áreas de deforestación, siendo reportada

principalmente en la región de Caatinga y Bosques. Una de las principales características de este género es que varias especies son ricas en componentes químicos de importancia para la medicina. De esta forma, esta revisión de la literatura, tiene como objetivo que los hallazgos sobre las actividades biológicas y la composición química de las especies de *Croton*. El presente estudio es una revisión de la literatura, realizada en las siguientes bases de datos: SciELO, BVS, MEDLINE, LILACS, PubMed y ScienceDirect, con un período de tiempo comprendido entre 1997 y 2020. inflamatorio, antihipertensivo, antifúngico, antimicrobiano, antidiabético, antioxidante, antinociceptivo y antiinflamatorio. En cuanto a los aspectos toxicológicos, los hallazgos sugieren precaución en el uso de especies de *Croton*, ya que algunas son tóxicas. Mientras que, en cuanto a la composición química, en la mayoría de especies se observa la presencia de varios metabolitos secundarios, como alcaloides, terpenoides, flavonoides y otros compuestos fenólicos. Por lo tanto, los resultados descritos en este artículo sugieren que la aplicación terapéutica de las especies de *Croton* está respaldada por la literatura, sin embargo, señalamos que se requiere precaución en el uso de las especies de *Croton*, algunas presentes por toxicidad.
Palabras clave: Croton sp; *Croton blancheantius*; Actividades biológicas; Composición química; Toxicología.

1. Introduction

Brazil has one of the greatest diversities of fauna and flora in the world and this biodiversity has a high economic value, because natural products can be used for a lot of purposes, since the food industry up to develop new therapeutic approaches (Souza *et al*., 2014). Natural products are considered one of the main sources that contribute to advances in health research, in such a way that obtaining new active principles and elucidating the action mechanism makes it possible for the industry to delineate new products, providing new applications, inputs and alternatives for the treatment of various pathologies. In the last years, great advances have been observed in the elucidation of compounds in plant species, being an essential premise to produce new therapeutic agents (Khan *et al*., 2018; Alves *et al*., 2019).

The Euphorbiaceae family comprising more than 8,000 species in approximately 334 genus, along the extension of the American territory it is possible to find about 2500 species distributed in 92 genus. In Brazil, 72 genus and about 1100 species are widely distributed in the tropical regions. There is a great diversity among species, ranging from shrub to tall tropical forest trees, but they are widespread across all types of vegetation. One of the main characteristics of Euphorbiaceae species is their plurality of applications in folk medicine, that demonstrate their variety of chemical constituents (Webster, 1987; Trindade et al., 2014).

Other's studies report that the phytochemical profile of species that comprise the Euphorbiaceae family comprises alcohols and hydrocarbons, in addition to phenolic compounds, such as flavonoids, lignin, coumarins, tannins, alkaloids, cyanogen glycosides and glucosinolates. It is considered one of the most important families due to the diversity of chemical compounds with biological activity (Seebaluck-Sandoram *et al*., 2017).

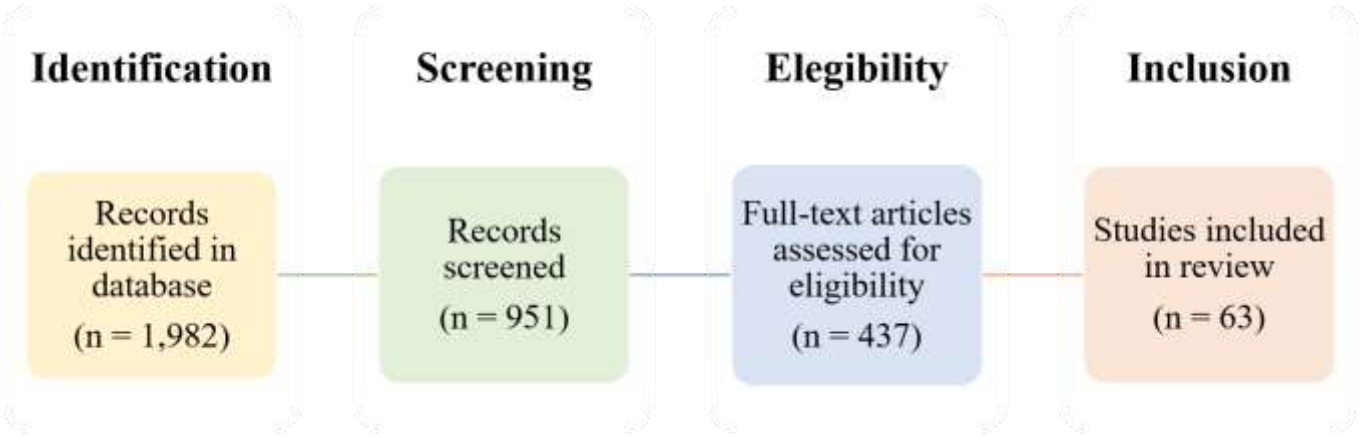
The Croton genus is one of the most diverse genus in the Euphorbiaceae family. In Brazil, there are about 356 species that belong to the genus, it is reported in the areas Caatinga, Atlantic Forest and Amazon Forest (Santos et al., 2005). The literature account that in Pernambuco it is possible to find about 35 species, most of which are distributed in the Caatinga (Silva *et al*., 2020). Described in the literature as a bush plant, which can regrow, especially in periods of rain, in way wildly, especially in deforestation areas, generally forming large homogeneous clusters in the Caatinga, that can reacher several (Trindade & Lameira, 2014).

A relevant feature is that several species of the genus are rich in volatile constituents (Santos et al., 2005). The literature reports several therapeutic activities for chemical compounds present in the Croton genus, including antinociceptive, anti-inflammatory, gastroprotective, antimicrobial, antispasmodic, antimalarial and antidiabetic (Fontenelle *et al*., 2008; Junior, Ladio & Albuquerque, 2011). In addition, the species are constantly used in folk medicine, in the form of infusion, and is indicated for the treatment of stomach pain, vomiting, diarrhea, hemorrhage, hemoptysis and swelling (Costa *et al*., 2012; Silva *et al*., 2021; Firmnino *et al*., 2019).

2. Methodology

A narrative literature review was carried out, according to Rother (2007), in which a scoping review is carried out by research in another way described with the objective of exploring as a review that already exists for a certain area of research, object identifying existing gaps, doing research, selecting, and synthesizing existing knowledge. This study is a literature review, carried out in several databases (SciELO, BVS, MEDLINE, LILACS, PubMed e Science Direct) and included original articles, books, dissertations, and theses. The main aspects related to the biological activities and chemical composition of the species published between 1997 and 2020 were considered. The keywords used were *Croton* sp; *Croton blancheantius*; quince; biological activities; chemical composition, toxicology. The flowchart of research and selection of articles are next, according Figure 1.

Figure 1. Flowchart of research and selection of articles.



Fonte: Autores.

3. Results and Discussion

3.1 Popular Use

The main species of the Croton genus found in Brazil and used in folk medicine is *Croton cajucara*, *C. blancheantius*, *C. celtidifolius* Baill., *C. palanostigma*, *C. schiedeanus* Schlech., *C. zehntneri* Pax, *C. eluteria* Bennett., *C. lechleri*, *C. palanostigma*, *C. urucurana*, *C. malambo* Karst e *C. nepetaefolius* Baill. (Pereira et al., 2002; Salatino et al., 2007; Fontenelle et al., 2008; Hort et al., 2012; Nascimento et al., 2017). The diversity of activities reported to the species of the genus are compiled in Table 1, according to the form of use of the plant and the region in which each species can be found in Brazil.

Table 1. Relationship between species, geographic location, and applications in folk medicine.

Species	Native	Applications in folk medicine	Reference
***C. blancheantius* Baill**	Brazilian Northeast	The infusion of the leaves is used for gastrointestinal disorders, rheumatism and migraine.	Firmino et al. (2019)
***C. cajucara* Benth**	Amazon forest region	The infusion of leaves, bark and stem is used to treat diabetes, control cholesterol and treat gastric and liver disorders.	Nascimento et al. (2017)
***C. celtidifolius* Baill**	Atlantic Forest (especially the southern region of Brazil)	The bark infusion is used in the treatment of inflammatory diseases, leukemia and rheumatism.	Hort et al. (2012)
***C. eluteria* (L.) W. Wright**	Northern region of Brazil	Its bark is used in powder form, with applications in the treatment of diarrhea, bronchitis and some people use it to treat fever.	Campagnuolo et al. (2005)
***C. lechleri* Müll.Arg**	Amazon forest region	Its red colored latex is used in the wound healing process.	Alonso-Castro et al. (2012)
***C. palanostigma* Klotzsch**	Atlantic Forest	Its latex is used as an antibiotic, in the treatment of diarrhea, gastric ulcers, intestinal inflammation and in some cases, in the treatment of cancer.	Maistro et al. (2013)
***C. malambo* H.Karst**	Northwest Region of the Amazon (Especially on the borders with Venezuela)	The infusion of the bark is used for analgesic purposes.	Bracho et al. (1966)
***C. urucurana* Baill**	Native to the Midwest	Used as healing and in cooking as a natural dye.	Silva et al. (2020)
***C. nepetifolius* Baill**	The cerrado	The peel decoction is used for antispasmodic and relief gas purposes.	Firmino et al. (2019)
***C. schiedeanus* Schltdl**	Northwest Region of the Amazon (Especially on the borders with Venezuela)	Leaf tea is used to treat hypertension.	Guerrero et al. (2004)
***C. zehntneri* Pax & K.Hoffm.**	Brazilian Northeast	The tea from the leaves and bark is used for a sedative effect.	Coelho-de-Souza et al. (2019)

Fonte: Autores.

3.2 Biological Activity

3.2.1 Antihypertensive activity

A study by Guerrero et al. (2001) reported that the aqueous extract of the leaves of the *Croton schiedeanus Schlecht* species associated with the drug phenylephrine can promote a synergistic effect, enhancing an antihypertensive activity. In 2004, Guerrero and colleagues evaluated the effectiveness of the aqueous extract of the same species in hypertensive mice and observed the effect of antihypertensive activity and bradycardia in animals, confirming the previous data.

Tests carried out with trans-dehydrocrotonin diterpene isolated from the bark of the stem *C. cajucara* concluded that the in vivo assay the diterpene promoted hypotensive and bradycardic effect, which were related to effect separate and independent vasorelaxant in the aortic endothelium. The results suggested that the hypotensive activity is not related to muscarinic, β-adrenergic stimulation or even to ganglionic blockade, however it is suggested that it may be related to the release of nitric oxide by the endothelium. With respect to bradycardia, the results indicated negative chronotropic effect resistant atropine (Silva et al., 2005).

Hort et al. (2012) in his studies conducted in mice, evaluated the fraction cardioprotective effect of proanthocyanidin of *C. celtidifolius* bark, the results demonstrated the prevention of LDL oxidation, in addition to reducing oxidative stress in

endothelial cells thus improving the cardioprotective role. In the in vivo results, successful in hypercholesterolemia mice, the fraction was able to prevent endothelial dysfunction, but was not able to reduce the extent of atherosclerotic lesion or reduce plasma lipid levels. In addition, they show that the fraction has a variety of effects by different mechanisms of action and working in cardiovascular protection.

Tufer et al. (2021) in their work, aimed to evaluate a diuretic activity of aqueous and methanolic extracts of *C. macrostachyus* leaves, their findings revealed that both extracts triggered diuresis, albeit at higher doses, however, it was also concluded that the aqueous extract showed better activity, due to having phytoconstituents responsible for the diuretic action that are more soluble in water. On the other hand, the analysis of biological fluids showed that the extracts have several modes of action, thus, it was possible to conclude that the extract of the species has diuretic activity and, consequently, it can be applied in the control of hypertension.

3.2.2 Anti-inflammatory and antinociceptive activity

Oliveira et al. (2001) carried out tests with essential oil obtained by steam drawing distillation of *Croton zehntneri* leaves in mice, to evaluate the antinociceptive effect, and their results concluded that the presence of the constituents anethole and β-myrcene are responsible for the activity, and the authors concluded that the oil exhibits an antinociceptive effect at doses well below the LD50 with a value of 2.5 g/kg orally.

Oliveira-Tintino et al. (2018) carried out tests with *Croton campestris* and proved that the presence of β-caryophyllene (15.91%) and 1.8-cineole (16.98%) in the essential oil are important for reducing edema in the evaluated model. The in vivo model assays of acute and chronic inflammation, with essential oil of *C. campestris*, concluded that the presence of β-caryophyllene demonstrated a significant anti-inflammatory activity, also inferring that the presence of 1,8-cineole was responsible for activity, and suggest that a mechanism of action by inhibition of cytokines occurs, in addition to describe that LD50 for oral administration was 5000 mg/kg.

The extract of *Croton matarensis* leaves arises from obtaining extracts with supercritical CO_2 (using different conditions, such as temperature and pressure variation) and was evaluated against in vivo anti-inflammatory activity. The extracts showed high levels of total phenolics and total flavonoids, while in the histopathological analysis of ischemic injury in the motor cortex of rats, the extracts showed influence on tissue reconstruction and cell density reduction, the treatment suggests a potential anti-inflammatory effect and neuroprotective, showing reduced injury in animals treated with SC-CO2 extract (Bezerra et al., 2020).

Martins et al. (2017) carried out tests with *Croton rhamnifolioides*, with the objective of evaluating the anti-edematogenic and anti-inflammatory effect of the essential oil of the leaf of *C. rhamnifolioides*, their results concluded that the major constituent 1,8-cineole was responsible for and regulating the changes and release of inflammatory mediators in rodents, therefore, suggesting that the essential oil has therapeutic potential for use in the development of new agents with anti-inflammatory activity.

3.2.3 Antimicrobial and antiprotozoal activity

Peres et al. (1997) evaluated the hydroethanolic extract and four fractions of the methanol extract of the stem bark of *Croton urucurana* Baillon, against *Staphylococcus aureus* and *Salmonella typhimurium* strains, the results suggested that the hydroethanolic extract and the hexane and hexane-dichloromethane fractions exhibited better activity against *S. aureus* when compared to *Salmonella typhimurium*, being the hexane-dichloromethane fraction with greater inhibitory effect against *S. aureus* (0.8 mg/mL).

Other tests were carried out with the crude aqueous and alcoholic extracts of the bark and leaves of *Croton roxburghii* Balak, against enteric pathogens causing urinary tract infections, and the results concluded that the extracts of the leaf bark were not successful against *Salmonella typhimurium*; however, the results were promising against *Staphylococcus aureus* and *Escherichia coli*. And the study also suggests that the alcoholic extract showed better activity when compared to aqueous extract (Panda et al., 2010).

Firmino et al. (2019) carried out in vitro tests to evaluate the inhibition of biofilm formation by oral mucosa bacteria, and the results indicated that the diterpenes isolated from *Croton blanchetianus* species reduced almost 100% of the biofilm, acting in the prevention and control of biofilm produced by *Streptococcus mutans* ATCC700610 and *Streptococcus parasanguinis* ATCC903.

Diaz et al. (2019) found that the ethanolic extract and the chloroform fraction of the leaves of *Croton lineares*, have poor activity against bacterial strains, however, antiprotozoal activity was known in both extracts. The authors concluded that the antiprotozoal activity is associated with the presence of apomorphine and flavonoid alkaloids, which were effective against *Trypanosoma cruzi*, with IC_{50} values between 1-26 μg/mL.

3.2.4 Antidiabetic activity

Kundu et al. (2020) evaluated the effect of the methanol extract of *Croton hookerio* leaves in streptozotocin-induced diabetic rats. The results suggested a considerable increase in the blood glucose level of the test animals when compared to the control group, in addition to demonstrating that the glucose levels in animals treated with the extract at a dose of 200 mg/kg and the positive control with metformin a 200 mg/kg, a significantly reduced was observed, thus suggesting that the extract has regulatory activity on blood glucose levels in diabetic rats. These results suggest that the methanol extract showed significant activity in the oxidative inhibition and inflammation, as it was observed that the extract reduced the glucose present in the blood circulation and improve renal histological damage frame and pancreatic having potential for application to treat diabetes.

3.2.5 Antioxidant activity

Tests with the bark of *Croton celtidifolius* show that the presence of flavonoids in the crude ethanol extract and fractions (butanolic and ethyl acetate) were able to inhibit deoxyribose, albeit at low rates (1 μg/mL). Other trials analyzed promoted phenolic compounds and subfractions and concluded that these in turn also have antioxidant properties, due to their ability to donate electrons and chelate metals. However, the results also showed that the aqueous fraction showed lower ability to inhibit the antioxidant activity, the authors suggest that this is due to the lipid system used in the experiment, which was biphasic, in which one phase is aqueous and the other lipids, with therefore, compounds which possess more hydroxyl end groups exerting greater antioxidant activity in the aqueous phase. These results corroborate the results compared with the lack of activity observed against the aqueous extract on the inhibition of liver homogenate oxidation *in vivo* (Nardi et al., 2003).

Lopes et al. (2004) evaluated the antioxidant activity of *C. lechleri* in *Saccharomyces cerevisiae* under conditions of oxidative stress. The results of this work demonstrate that the sap of *C. lechleri*, when compared 10 min before treatment, satisfactorily inhibits the cytotoxic effect of the aporphinoid alkaloid in haploid yeast cultures, this inhibition was observed both in the absence and in the presence of growth cell phone, however, this effect is more pronounced in exponentially growing cells. However, it was noticed that after the treatment with hydrogen peroxide, it was only possible to observe the significant antioxidant effect in the stationary growth phase.

Other studies have shown that two of the clerodane-type diterpenoids, which were isolated from the dichloromethane fraction of *Croton hypoleucus*, crotonpene hypolein, also showed antioxidant activity by the in vitro test with the crude extract. The results showed that the extract was able to eliminate the DPPH radical and reduce Fe^{+3}, mechanisms that suggest a

reduction in the oxidative effect, in addition to helping to reduce the liver, thus demonstrating the potential of the genus (Urrutia-Hernández et al., 2019).

Rocha et al. (2021) carried out tests with the objective of evaluating the antioxidant potential of the ethanol extract and fractions of the species *Croton betaceus* and *Croton lundianus*. The results of the phytochemical prospection showed that the extract and fractions contain all studied compounds (flavonoids, steroids, tannins, saponins and triterpenes), except for the alkaloid class. Evaluation of antioxidant potential of the ethanol extract and fractions *C. betaceus* and *C. lundianus* occurred through reductive plasma iron capacity tests (FRAP) and DPPH elimination ability, the results showed activity in all fractions of both species, especially in the hexane fraction. However, in general, the results suggested that *C. betaceus* fractions have higher antioxidant potential than *C. lundianus* fractions. The authors enhanced that this antioxidant potential is due to the high content of flavonoids present.

3.2.6 Antitumor activity

Studies performed with the extracted sap from *C. lechleri* evaluated the inhibition potential across the cell line of human melanoma (SK23) and colon cancer (HT29), the results of the sap possess antiproliferative activity on both cell lines in vitro. In addition to describing an induction of SK23 cell apoptosis, which would be suggestive of a new source of potential anticancer agents (Montopoli et al., 2012).

Li et al. (2017) evaluated the antitumor potential of *Croton tiglium* extract, against A549 cells that cause lung cancer in humans, and concluded that the extract has a significant inhibitory effect on cell proliferation. These data corroborate the results of Bhavana et al. (2016), in their studies observed that the acetone extract from the leaves of *C. bonplandianus* (Baill) was able to induce cell death in the human lung cancer cells.

Assays performed with the ethanol extract of leaves of *C. bonplandianus* (Baill) against hematologic cancer cells of cell line chronic myeloid leukemia (K562) and Raji cells, demonstrated an effect on cells inhibitor of cells, then results demonstrate that the K562 cells was more sensitive than Raji cells, the authors reported that phytochemicals present in the species are responsible for this antitumor activity (Suresh et al., 2020).

3.3 Toxicity

Tests performed in male Wistar rats with volatile oil of *Croton zehntneri* in order to investigate systemic toxicity, observed some morphological changes in the organs, but there was no induction of structural abnormalities in the organs, and with this, the findings suggest that doses with concentrations below 250 mg/kg offer a low toxicological risk (Oliveira et al., 2001; Sousa et al., 2005). Compagnone et al. (2010) in their studies evaluated the in vitro the cytotoxicity of essential oil from leaves of *C. matarensis* against three different human cancer cell lines, colon adenocarcinoma, cervical carcinoma and fibroblasts, the results describe that, the CI_{50} assays obtained the respective values: 36.60, 83.90 and 132.73 μg/mL, these findings suggest regular cytotoxicity.

Maistro et al. (2013) conducted tests on mice to investigate the chemical components and to evaluate the toxic effect of the aqueous extract of *Croton palanostigma*, the tests concluded that the main chemical component taspine one alkaloid present in the crude sap showed genotoxic effects in liver cells, on this way, concluding that the sap should be used with caution. Shantabi et al. (2020) using the ethanol extract of *C. caudatus* in tests with HeLa cells, with purpose to observe a toxicological response, concluding that the ethanol extract increases lipid peroxidation and the release of lactate dehydrogenase, relating cell death to the possibility of formation of free radicals, consequently increased DNA damage and cell apoptosis.

Studies on toxicity with a type of *C. urucurana*, carried out by Silva et al. (2020) obtained as a result an increase in liver enzyme activity, a decrease in fetal body weight and an increase in proteins and cholesterol in the bloodstream, and a significant increase in heart weight, in addition to contributing to the development of fetal skeletal abnormalities. Freitas et al. (2020) evaluated the toxicity and genotoxicity of the ethanolic extract of *C. blanchetianus*, its description, that the extract requires safety for oral use, but triggered some biochemical, hematological, and histological changes when administered intraperitoneally, in the case of genotoxicity, the findings describe that at all doses and times tested, no formation of micronuclei was observed, in this way, suggesting that the extract is not harmful.

Cruz et al. (2020) evaluated the toxicological potential of selected essential essentials from the leaves of *C. argyrophyllus* and *C. tetradenius* in mice, the results describe that when associated and administered intraperitoneally, they have a medium degree of toxicity, so caution is necessary, however when administered orally no toxicity was observed, therefore the authors stated that the application for use in mammals is safe, these described corroborate the good results obtained by Carvalho et al. (2016), that in their studies as the essential oil of *C. tetradenius*, observed that when administered in mice by orally it did not show toxic aspects, but when administered intraperitoneally it triggered clinical signs and even led to the death of animals in studies, what they described as potentially toxic.

3.4 Chemical composition

Phytochemical studies with species of the Croton genus demonstrated that in most species, it is possible to observe the presence of several secondary metabolites, such as alkaloids, terpenoids, flavonoids and other phenolic compounds. Among the constituents, terpenoids are the most widespread and most relevant to the genus (Salatino et al., 2007).

By gas chromatography, Peres et al. (1997) evaluated the methanol extract from the leaves of *C. urucurana*, and observed the presence of acetyl aleuritolic acid, β-sitosterol and sonderianin diterpene, and identified the presence of the steroids stigmasterol, β-sitosterol and campesterol. In phytochemical studies on the species *C. macrostachyus* performed with the ethanolic extract of roots showed the presence of fatty acids, β-sitosterol, stigmasterol, lupeol, betulin and cyclohexene diepoxide. While the roots were found traquiloban acid ent-19-oic acid and then traquiloban--18-oic acid; and the analysis of the shell was observed the presence of terpenoid, lupeol, betulin and crotepoxide (Kapingu et al., 2000; Tene et al., 2009).

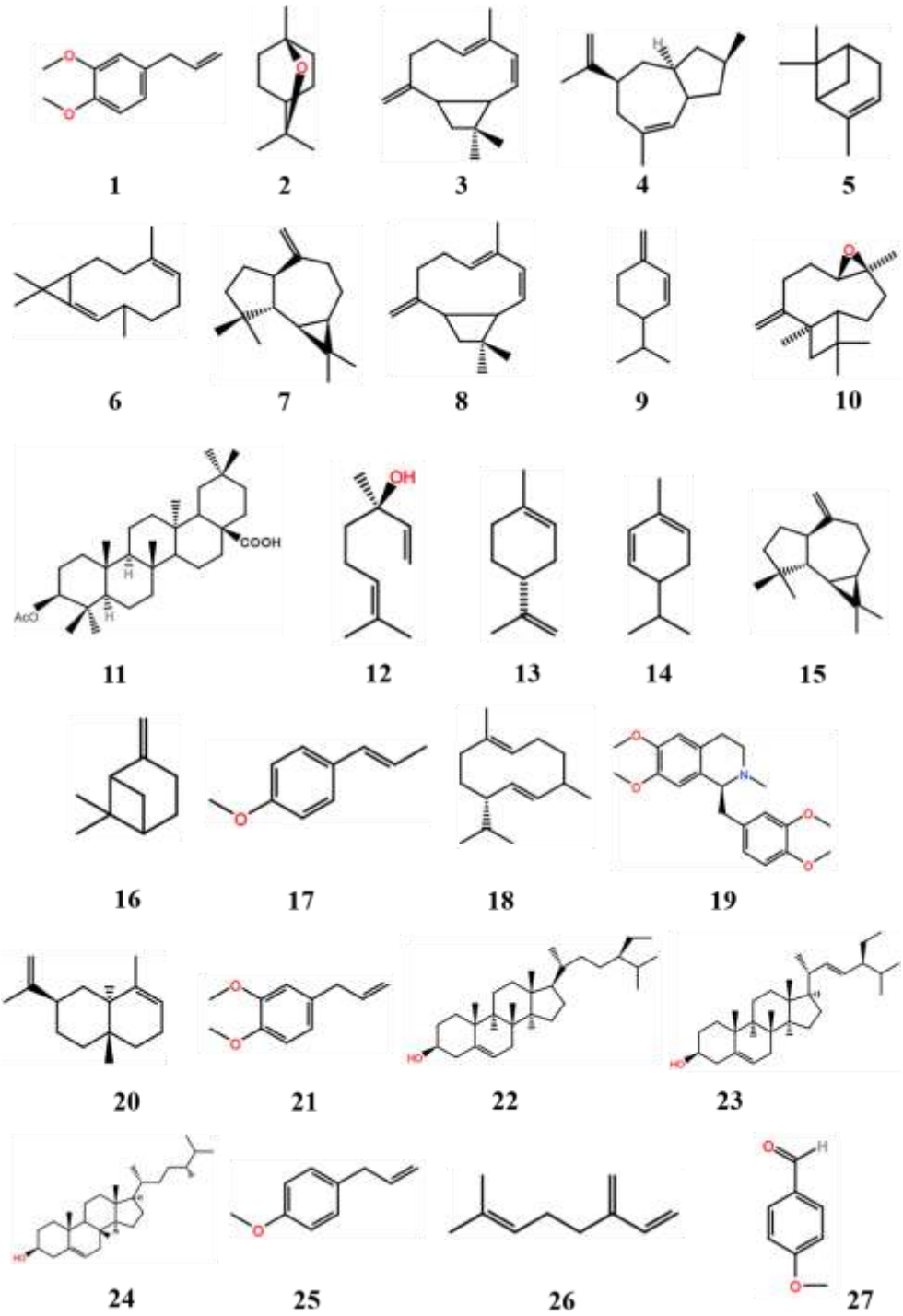
Righi et al. (2013) performed gas chromatography tests coupled with mass spectrophotometry with the ethanol extract of leaves from the *C. sphaerogynus*, and demonstrated that this specie is rich in terpenoids, of which triterpenoids stand out, observing a presence even in minors of clerodane-type diterpenes. Alencar Filho et al. (2017) performed tests to evaluate a variation of the essential composition of *C. heliotropiifolius* in different seasons of the year, among the main constituents found, β-caryophyllene was evidenced, which showed a greater variation, having a concentration in winter of 46.99 %, while in the summer it was 28.61%. The studies also evidenced the presence of terpenes, such as: bicyclogermacrene, germacrene and 1,8-cineole.

The chemical composition of the essential oil of *C. zehntneri*, evaluated by gas chromatography coupled with mass spectrometry, obtained as results the presence of trans-anethole (85.7%), estragole (4.8%), 1,8-cineole (2.95%), β-myrcene (2.2%), anisaldehyde (1.22%), trans-caryophyllene (0.9%), and some unidentified compounds (2.23%) (Coelho-de Souza et al., 2019). Diaz et al. (2019) performed a characterization of the ethyl acetate fraction of *Croton linear* by high performance liquid chromatography, and identified seven new compounds for the specie, the alkaloids laudanidin, laudanosine, reticulin, coridin, glaucine and cularin, and glycosylated flavonoids.

Ribeiro et al. (2020) identified 54 compounds in the essential oil of *C. rudolphianus*, among the main findings, 40.9% were from an unknown compound, that has not been elucidated, however in the constituents elucidated, the presence of

spathulenol, bicyclogermacrene and eugenol was observed. In this way, the diversity of chemical compounds reported for the species of the genus is shown in Figure 2, according to the species, structure, and part of the plant.

Figure 2 – Terpenes described for the species of the genus *Croton*.



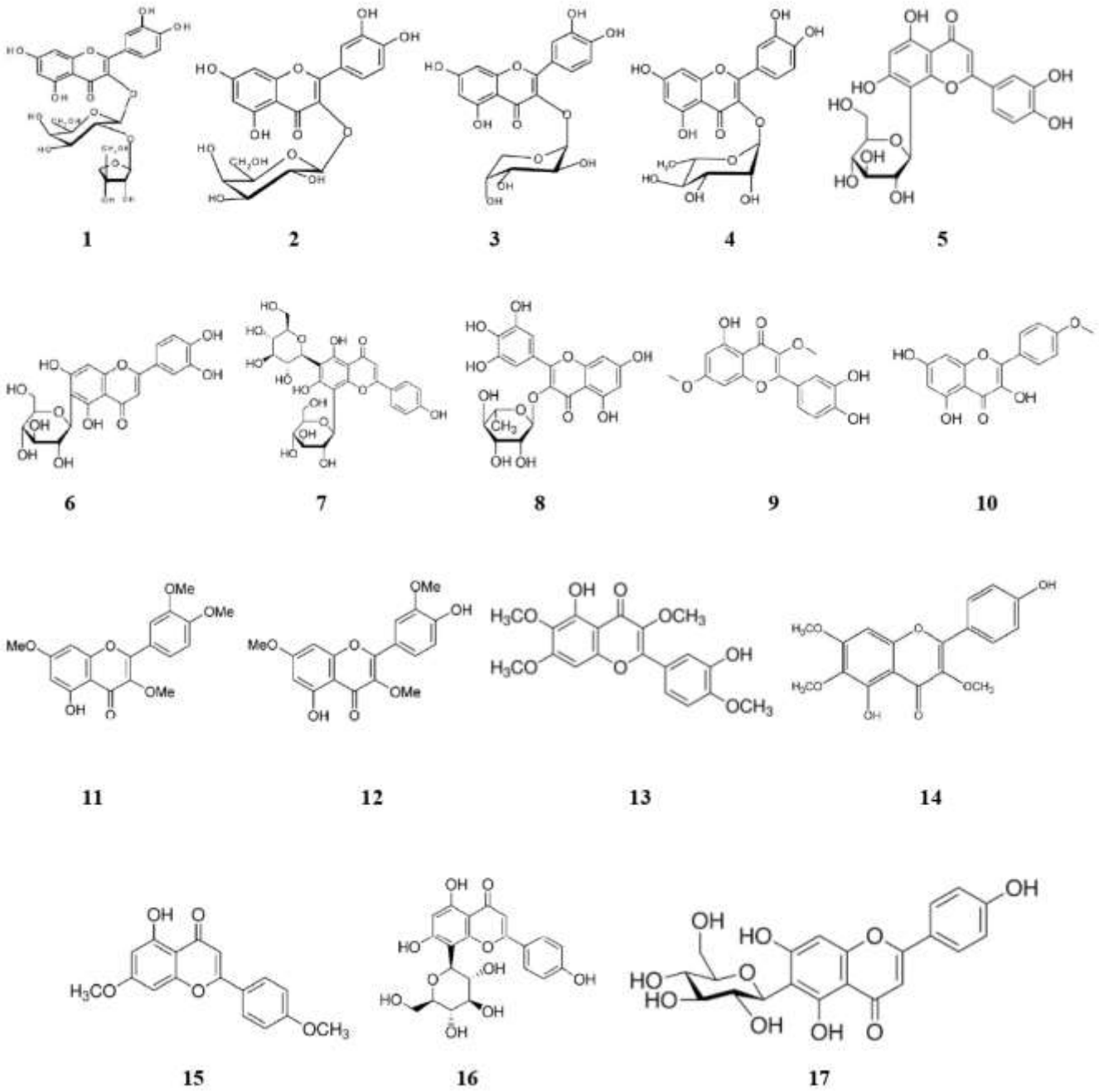
Terpenes described for the species of the genus *Croton*. 1. Methyleugenol; 2. 1,8-Cineol; 3. (E)-caryophyllene; 4. β-guaiene; 5. α-pinene; 6. Bicyclogermacrene; 7. Spatulenol; 8. β-felandrene; 9. β-myrcene; 10. Caryophyllene oxide; 11. Acetyl aleuritolic acid; 12. Linalool; 13. Limonene; 14. α-felandrene; 15. Spatulenol; 16. β-pinene; 17. Trans-anethole; 18. Germacrene D; 19. Laudanosine; 20. α-selinene; 21. Methyleugenol; 22. β-sitosterol; 23. Stigmasterol; 24. Campesterol; 25. Estragol; 26. β-myrcene; 27. Anisaldehyde.
Croton adamantinus (Leaves) [61]; *C. argyrophylloides* (Aerial parts) [28]; *C. argyrophyllus* (Aerial parts) [62]; *C. cajucara* (Aerial parts) [19, 63]; *C. campestres* (Aerial parts) [26]; *C. conduplicatus* (Aerial parts) [26]; *C. cordiifolius* (Aerial parts) [61]; *C. ericoides* (Aerial parts) [37]; *C. growioides* (Aerial parts) [64]; *C. heliotropiifolius* (Aerial parts) [44]; *C. isabelli* (Aerial parts) [46]; *C. micans* (Aerial parts) [43]; C. nepetifolius (Aerial parts); *C. pullei* (Aerial parts) [53]; *C. sonderianus* (Leaves) [28]; *C. urucurana* (Leaves) [30]; *C. zehntneri* (Leaves) [64,24]. Fonte: Autores.

Other studies describe the presence of flavonoids in some species of the genus, the tests carried out by Santos et al., (2005) describe the identification of four O-glycosylated flavonoids found in *C. campestris* leaves, 3-O-β-D-apiofuranosil-(1→2)-galactopyranosyl quercetin, 3-O-β-D-galactopyranosyl quercetin (hyperin), 3-O-α-L-arabinopiranosil quercetin (guaijaverin) e 3-Oα-L-rhamnopyranosyl quercetin (quercitrin). Coelho et al., (2016) describes that the leaves of the species *Croton betulaster* have three types of flavonoids, which are, 5,3′-di-hidroxi-3,6,7,4A′-tetramethoxyflavone (casticin), 4′-di-hidroxi-3,6,7-trimethoxyflavone (penduletin) e 5-hidroxi-7,4′-dimethoxyflavone (dimethoxyflavone).

The findings of Wagner et al., (1970) describes five C-glycosylated flavonoids for the aerial parts of *C. zambezicus* species, in special at leaves, which are, vitexin, suponeretin, orientin, isoorientin and cicenin-2. Salatino et al. (2007) describes in their essays that isolated 3-O-α-L-rhamnopyranoside from *C. draco* leaves (myricitrin), this same flavonoid was described by Kostova et al. (1999) that are present in *C. panamensis* leaves. Maciel et al. (2000) carried out studies with *Cm cashew* leaves and in their results, observed the presence of kaempferol-3-4′,7-trimethyl ether (Kaempferide). The latter, in turn, was also described by Guerrero at al. (2002) in your studies with the roots of the species of *C. curiosus* and *C.saltensis*, that used the leaves to make EtOH extract, for elucidation of the compounds.

González-Vázquez et al. (2006) do some studies with the hexane extract with *C. ciliatoglanduliferus* leaves, which as a result brought the elucidation of two flavonoids, they are ,5,4′-dihydroxy-3,7,3′-trimethoxyflavone (pachypodol) and 5-hydroxy-3,7,3′,4′-tetramethoxyflavone (retusin). Other studies with the shoots of *C. schiedeanus*, demonstrated that they contain quercetin-3,7-dimethyl ether (Guerrero et al., 2002). In this way, the flavonoids described are shown in the Figure 3, according to the species, structure, and part of the plant.

Figure 3 – Flavonoids described for the species of the genus *Croton.*



Flavonoids described for the species of the genus *Croton*. 1. Hyperin; 2. (3-O-β-D-apiofuranosil-(1→2)-galactopyranosyl); 3. Guaijaverin; 4. Quercetin; 5. Orientin; 6. Isoorientin; 7. Vicenin-2; 8. Myricitrin; 9. Kaquercetin-3,7-dimethyl ether; 10. Kaempferide; 11. Retusin; 12. Pachypodol; 13. Casticin; 14. Penduletin; 15. Dimethoxyflavone; 16. Vitexin; 17. Suponeretin. *C. campestris* (Leaves) [7]; *C. betulaster* (Leaves) [52]; *C. zambezicus* (Aerial parts) [57]; *C. draco* (Leaves) [15]; *C. panamensis* (Leaves) [58]; *C. cashew* (Leaves) [59]; *C. curiosus* (Roots) [18,19]; *C. saltensis* (Roots) [19]; *C. schiedeanus* (Leaves) [18]; *C. ciliatoglanduliferus* (Leaves) [60].

4. Conclusion

The data presented in this review on *Croton* species reflect a compilation of knowledge about their chemical composition and biological properties already elucidated. The *Croton* genus is widely used by folk medicine, and as information proves some activities, such as anti-inflammatory, anti-hypertensive, antifungal, antimicrobial, antidiabetic,

antioxidant, antinociceptive and antitumor. However, the results described in this article suggest that caution is needed in the use of Croton species, as some of them are toxic. In view of this, in-depth studies are needed to correlate biological activities with chemical composition.

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