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An update on phytochemistry and pharmacology of *Croton malambo* H. Karst

Actualización de la fitoquímica y farmacología de *Croton malambo* H. Karst

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Abstract

The genus *Croton* is one of the most characteristic groups of plants belonging to the Euphorbiaceae family. Under this genus is *Croton malambo* H. Karst, a tree found in the Guajira peninsula, shared by Colombia and Venezuela. The inhabitants of this region have used this plant as a treatment for rheumatism, body pain, wounds, bumps, local inflammation, dermal infection, toothache, umbilical infections, headaches, and bronchitis. This short review provides traditional knowledge, phytochemistry, and pharmacological studies of *C. malambo*. The literature reviewed for this article was obtained from the Web of Science, PubMed, ScienceDirect, and Google Scholar research published before March 2023, and own results. Phytochemical investigations reveal that the plant is a rich source of triterpenes, phenyl compounds, lignans, ent-kauranes, alkaloids, monoterpenes, and volatiles. The results of pharmacological tests on this plant indicate antidiabetic, antimicrobial, anti-inflammatory, antinociceptive, and anticancer effects. This paper resume information on the phytochemical constituents and the pharmacological studies on extracts, compounds, and volatiles on *Croton malambo*. The purpose of this review is to stimulate future research that insides the potential of this species to obtain new medicinal agents in important diseases like diabetes and cancer.

Keywords: *Croton malambo,* traditional uses, phytochemical constituents, pharmacological studies

Resumen

El género *Croton* es uno de los grupos de plantas más característicos de la familia Euphorbiaceae. Bajo este género se encuentra *Croton malambo* H. Karst, un árbol que se encuentra en la península de la Guajira, compartida por Colombia y Venezuela. Los habitantes de esta región han utilizado esta planta como tratamiento para el reumatismo, dolor corporal, heridas, golpes, inflamación local, infección dérmica, dolor de muelas, infecciones umbilicales, dolor de cabeza y bronquitis. Esta breve revisión proporciona conocimientos tradicionales, fitoquímica y estudios farmacológicos de C. malambo. La bibliografía revisada para este artículo se obtuvo de las investigaciones de Web of Science, PubMed, ScienceDirect y Google Scholar publicadas antes de marzo de 2023 y resultados propios. Las investigaciones fitoquímicas revelan que la planta es una rica fuente de triterpenos, compuestos fenólicos, lignanos, ent-kauranos, alcaloides, monoterpenos y aceites esenciales. Los resultados de pruebas farmacológicas sobre esta especie indican efectos antidiabéticos, antimicrobianos, antiinflamatorios, antinociceptivos y anticancerígenos. Este artículo resume la información sobre los constituyentes fitoquímicos y los estudios farmacológicos sobre extractos, compuestos y volátiles de *Croton malambo*. El propósito de esta revisión es estimular futuras investigaciones que profundicen en el potencial de esta planta para obtener nuevos agentes medicinales en enfermedades importantes como la diabetes y el cáncer.

Palabras clave: *Croton malambo,* usos tradicionales, constituyentes fitoquimicos, estudios farmacolygicos

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Introducción

Croton genus belongs to the Euphorbiaceae family, one of the biggest in the plant kingdom; this consists of herbs, shrubs, and trees and, although less common, some appear as lianas. *Croton* is the largest genus of the Crotonoidae subfamily (Caruzo *et al.*, 2011), under its classification, have been reported approximately 1200 species distributed widely in tropical and subtropical regions of the continents (Berry *et al.*, 2005). In Venezuela, 79 species have been identified (Berry and Riina, 2008). Many species of this genus are endowed with medicinal properties, especially those that exudate red latex, for which some species are known as "sangre de drago". The folk medicine of countries in Asia, Africa, and America had been used *Croton* species to treat, inflammations, diabetes, rheumatism, healing wound, and gastric illness, and as an analgesic agent (Salatino, 2007; Abega *et al.*, 2014; Langat *et al*, 2020; Bezerra *et al.*, 2020, Luu-dam *et al.*, 2023).

Regarding the chemistry of *Croton* species, it is a rich genus in secondary metabolites, where families of compounds like alkaloids, flavonoids, glycosides, and terpenoids are common; between the terpenes, the diterpenes are the more important compounds in this classification, being clerodanes, tiglianes, kauranes, cembranes, labdanes, and crotofolanes the common structures in many species (Xu *et al.*, 2018; Shi *et al.*, 2018).

Croton malambo H. Karst is a medium size tree that grows in the Venezuelan northwest region and in the northern part of Colombia, it is known by the folkloric names of palomatías, malambo, torco, and cáscara de lombrices, its bark and leaves expel a pleasant aroma. Traditional uses of *C. malambo* have been documented by the people who inhabit the region where it grows, especially the Wayuu ethnic group, inhabitants of the Guajira peninsula, shared by Venezuela and Colombia (Figure 1). These people, maintain an ancient and rich culture in traditions and, folk medicine (Figures 2 and 3), the Wayuu, include this tree as one of the more used plants, to treat diverse illnesses and diseases. The traditional uses document the forms of poultices, baths, and plasters to treat rheumatism, body pain, wounds, bumps, local inflammation, dermal infection, toothache, umbilical infections, headache, and bronchitis. Drinks are used in disorders that can include dysphonia, tonsillitis, fainting, diabetes, diarrhea, stomach pain, belly pain, indigestion, difficulty labor, retained placenta, colds, and cough. Bark, leaves, and the whole plant are among the most commonly used parts of this species (Rosado *et al.*, 2010; Tillett *et al.*, 1997; Garcia-Barriga, 1992).

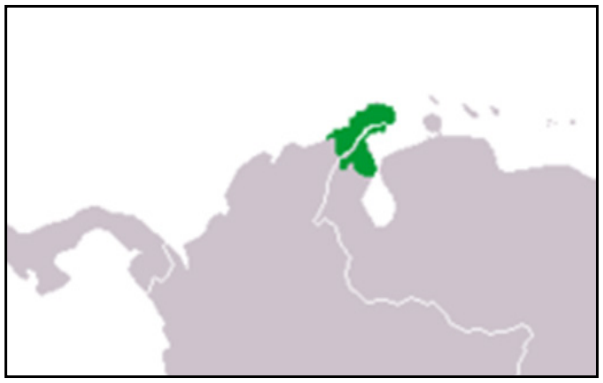

Figure 1. Guajira peninsula showed in green color. Taken from https://es.wikipedia.org/wiki/Pueblo_way

This communication attempts to show an update on the phytochemical and pharmacological studies of *Croton malambo* (CM), which demonstrates its reputed medicinal uses and its therapeutic potential for future research.

Figure 2. Wayuu women with their typical costumes. Taken from https://venezuelaenarte.com

Figure 3. The yonna, a traditional dance native to the Wayú people, is also known as chichamaya. Taken from https://es.wikipedia.org/wiki/Pueblo_way

Phytochemistry

Croton malambo contains triterpenes, phenyl compounds, lignans, ent-kauranes, alkaloids, monoterpenes, and volatiles. The structures of these compounds are shown in Figures 4 and 5, and the pharmacological actions of these secondary metabolites are described in continuation. The major compound isolated from phytochemical studies of bark is t-dehydrocrotonin (1), a clerodane diterpene with relevant biological activities (da Costa *et al.*, 2007): hypoglycemic and hypolipidemic (Silva *et al.*, 2001), antigenotoxic (Agner *et al.*, 1999), antiulcerogenic (Rodriguez *et al.*, 2004), anti-inflammatory, antinociceptive (Perazo *et al.*, 2007), antiestrogenic (Luna-Costa *et al.*, 2007), cardiovascular (Silva *et al.*, 2005), antitumor (Grynberg *et al.*, 1999; Melo *et al.*, 2004), and trypanocidal (Campos *et al.*, 2010). Cajucarinolide (2) and isocajucarinolide (3) also belonging to the clerodanes diterpenes class, have been reported to have anti-inflammatory activity (Ichihara *et al.*, 1992). Other major compounds isolated from *C. malambo* bark are methyleugenol (4), a well-known monoterpene endowed with diverse pharmacological actions, antinociceptive effect (Yano *et al.*, 2006), anesthetic (Wang *et al.*, 2015), relaxant and antispasmodic (Lima *et al.*, 2000), anticancer (Yin *et al.*, 2018), and also with cardiovascular effects (Lahlou *et al.*, 2004). Methyleugenol (4), isoelimicine (5), and δ-cadinol (6) are present in the bark. The triterpene lupeol (7) is recognized with several biological properties such as anti-inflammatory, antitumor, antiprotozoal, and antimicrobial (Gallo and Sarachine, 2009), it is present in barks and leaves, also another ubiquitous triterpene, betulin (8) was found in the bark, this metabolite had been well investigated by their pharmacological actions: anti-HIV, antitumor, antimalarial, anti-inflammatory, infectious diseases, metabolic and cardiovascular disorders (Amiri *et al.*, 2020; Sami *et al.*, 2006). The stigmasterol was also present among the constituents of *C. malambo* barks (9), this sterol had been recognized with several biological activities on different metabolic disorders as anticancer, anti-osteoarthritis, anti-inflammatory, anti-diabetic, immunomodulatory, antiparasitic, antifungal, antibacterial, antioxidant, and neuroprotective properties (Bakrim *et al.*, 2022).

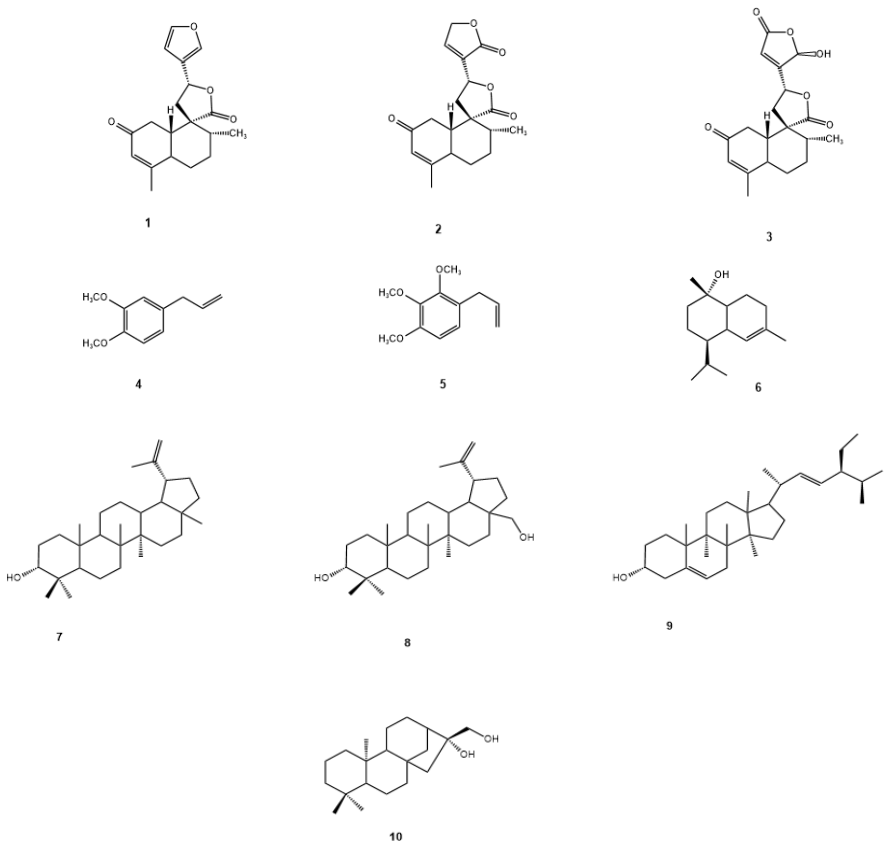

Figure 4. Isolated compounds from *Croton malambo* barks

Finally, the diterpene, 16α, 17β-diol-entkaurane (10) showed cytotoxicity and proapoptotic activity in human mammary carcinoma (Morales *et al.*, 2005) through a mechanism that includes Bcl-2 disruption of the Ap-2a/Rb transcription activating complex and induction of E2F1 up-regulation in MCF-7 cells (Morales *et al.*, 2011).

Those secondary metabolites previously described were isolated from *C. malambo* barks (Suárez, 2000), later the leaves were submitted to a phytochemical study, and a series of diterpenes isolated (Figure 5), the neo-clerodane ent-15,16-dihydroxy-cleroda-3,14-diene (11), ent-15,16-kauren-17-ol (12) and, 5-hydroxy-cis-dehydrocrotonin (13) which were evaluated as antibacterial and cytotoxic (Suárez *et al.*, 2014), and the bioactive glutarimidic alkaloids julocrotol (14) and julocrotone, being reported by us with anti-inflammatory properties (15) (Suárez *et al.*, 2004; Mijares *et al.*, 2012) were also isolated from the leaf (Suárez *et al.*, 2014).

Pharmacology

An aqueous extract of *C. malambo* bark from Venezuela was evaluated in an animal test for acute toxicity, anti-inflammatory and antinociceptive activity, results are indicated here.

Acute toxicity

The TD_{50} was determined according to Litchifield and Wilcoxon (1949) and acute toxicity was determined in mice. Different groups of animals were treated with a physiological solution and with increasing doses of *C. malambo* aqueous extract, in an intraperitoneal way. The LD_{50} and TD_{50}

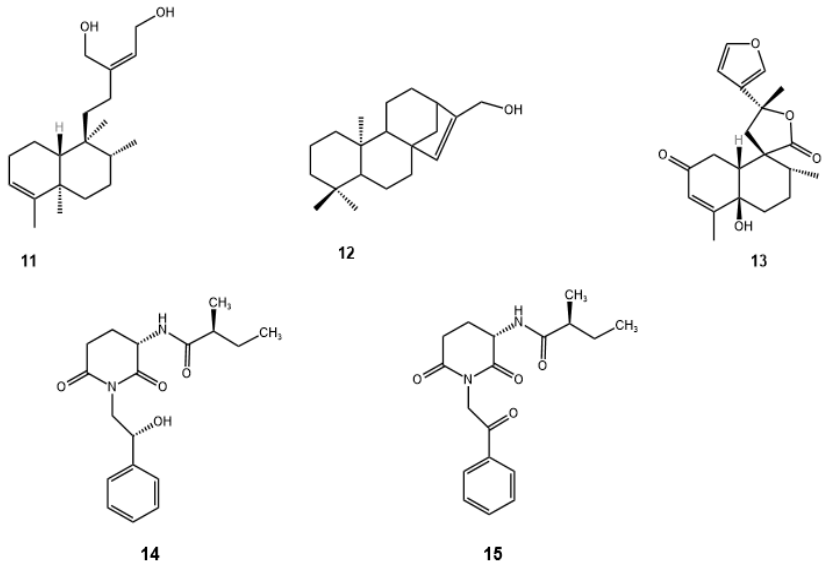

Figure 5. Isolated compounds from *Croton malambo* leaf

were obtained, and stereotypy was chosen to determine the TD_{50} because it was the most representative toxic effect observed in this test. At the highest dose tested, 4096 mg/kg, no mortality was observed (Suárez *et al.*, 2003)

Anti-inflammatory activity

To determine anti-inflammatory activity extract in rats, Winter *et al.* (1963) protocol was followed. Animals were divided into groups and pretreated with a physiological solution, acetylsalicylic acid, sodium diclofenac, and aqueous extract of *C. malambo*, by intraperitoneal (i.p.) treatment. Thirty minutes after treatment, 0.1 mL of an albumin solution 0.5% (w/v) was injected into the left hind paw of each rat. The volume of each treated leg was determined every 30 min up to 240 min using a plethysmometer.

Antinociceptive activity in mice

The antinociceptive activity of aqueous bark extract was assayed by thermal and chemical methods in experimental animals. Details and results of these assays are given below.

Thermal method

The antinociceptive effect, expressed as the time required for mouse tail flick after exposure to a source of radiant heat, was evaluated according to Davies (1946). Animals were divided into groups, and treated as follows with physiological solution (Control group); acetylsalicylic acid (200 mg/kg, p.o.); morphine hydrochloride (3 mg/kg, i.p.), and with *C. malambo* aqueous extract (6 mg/kg, i.p.), respectively. Animals were exposed to radiant heat up to a maximum of 15s. The time required for mice tail flick was considered as the reaction time. Reaction time was recorded at 15, 30, 60, and 90 min after each treatment.

Chemical method

The animals' groups for this experiment were pretreated as follows: physiological solution (0.9%; 10 mL/kg, i.p.) (Control group); morphine hydrochloride (3 mg/kg, i.p.); acetylsalicylic acid (200 mg/kg,

p.o.); *C. malambo* aqueous extract (6.15 mg/kg, i.p.). At the time of peak effect for each drug, animals were treated with phenyl quinone (3mg/kg), and the number of animals presenting writhing syndrome, which consists of the contraction of the abdominal area with an extension of hind legs, was recorded.

The results obtained with the above-described experiments demonstrate that *C. malambo* bark aqueous extract has antinociceptive and anti-inflammatory effects. TD_{50} was determined to be 12.3 mg/kg (95% CI: 10.3-14.6 mg/kg). Because lethal effects were not observed at any of the administered doses, it was not possible to determine LD_{50} even at the highest dose tested. The results also demonstrate that *C. malambo* aqueous extract, reduced albumin-induced paw edema. Anti-inflammatory activity remained for the whole experimental period, and this effect was considered like that produced by acetylsalicylic acid. Data concerning antinociceptive effect indicated *C. malambo* aqueous extract produced a significant increase in mice reaction time in tail flick experiments which was maximum at 90 min. It revealed a considerable effect for treatment groups. *C. malambo* aqueous extract was effective in inhibiting phenyl quinone-induced writhing syndrome in mice (50% respect to control). This effect was similar to that produced by ASA and less than that caused by morphine (84%). The study suggests that this plant extract possesses an antinociceptive and an anti-inflammatory effect.

Antiproliferative activity

In a work screening of a few medicinal plants from the Colombian Caribbean, an alcoholic extract of *C. malambo* was evaluated, and the antiproliferative action against cancer cells, H292 (mucoepidermoid carcinoma), and A549 (lung adenocarcinoma) was determined by the MTT method. The extract only showed moderated activity on H292 cells (Caro-Fuentes *et al.*, 2019),

Antidiabetic activity

Studies from our lab have shown the hypoglycemic and hypocholesterolemic activity of this plant in rats. The effect of the *C. malambo* aqueous extract on glucose-6-phosphatase (G6P) activity was realized in an animal model of diabetes-induced with alloxan. Results showed that *C. malambo* aqueous extract decreases enzyme activity depending on dosage and suggests that the extract may produce its hypoglycemic action through the restoration of the Langerhans islets (Suárez *et al.*, 2022, unpublished results).

Essential oils

The essential oils of barks and the leaf of *C. malambo* are a complex mixture of different compounds. The analysis of the *C. malambo* oil extracted from the barks of plants growing in Venezuela showed 36 constituents including traces, in which methyl eugenol (65.4%), methyl isoeugenol (6.3%), elemicine (4.7%), isoelemicine (3.4%), veratral (3.0%) and δ-cadinol (4.1%) were the major components (Suárez *et al.*, 2005) (Figure 3). The composition of the essential oil obtained from the leaves of these plants was also investigated, the major compounds present in this oil were found to be methyl eugenol (94.2 %); γ-bisabolene (1.3 %), isoelemicin (0.8 %) and γ-curcumene (0.8 %) were the minor compounds (Suárez *et al.*, 2008).

Other investigations of *C. malambo* from Colombia, have shown similar compounds with different concentrations, but in all of them, the major compound is methyleugenol (Jaramillo *et al.*, 2010; Jaramillo *et al.*, 2007; Muñoz-Acevedo *et al.*, 2014). In a study that described different extraction techniques for oil isolation, the results regarding the main components demonstrated previous findings (Jaramillo-Colorado *et al.*, 2014).

Pharmacology of essential oils

In recent years, pharmacological studies in Colombia have been conducted to explore the beneficial effects of *C. malambo* essential oils. Studies have shown antioxidant (Jaramillo *et al.*, 2010), acarycidal (Mendoza-Meza *et al.*, 2007), repellent, cytotoxic properties (Fuentes *et al.*, 2017), and acute toxicity against *Artemia salina* (Jaramillo *et al.*, 2007).

Antioxidant activity

The chemical composition of essential oils from plants of *C. malambo* growing in Colombia was investigated, and methyl eugenol (ME) was found to be the major compound. Determination of antioxidant activity was achieved using a discoloration assay of the stable radical cation ABTS+. The results indicated low antioxidant activity of the essential oil (Jaramillo *et al.*, 2010).

Cytotoxic activity

Another research from Colombia examined the chemical composition and the cytotoxicity of the total oil of leaves and branches of *C. malambo*, and the major compounds methyl eugenol and eugenol. They were submitted to assays of lymphocytes cytotoxicity test, and the results indicated a moderated cytotoxicity for the total oil, and the major components methyleugenol and eugenol, with LC_{50} values between 310 ± 17 – 897 ± 11 μg/mL, the authors mention that the pure essential oil of leaves was (310 ± 17), essential oil of branch (311 ± 5), methyleugenol (584 ± 34), and the more toxic was eugenol (897 ± 11). The toxicity *in vivo* was also investigated on Zebra fish embryos, the results showed that the most toxic in this assay was the eugenol with LC_{50} value (43 ± 9), followed by the essential oil of branches (28 ± 6) and methyleugenol (16 ± 9) (Muñoz-Acevedo, 2014).

Acute toxicity

The acute toxicity of an oil sample of *Croton malambo* plants, growing in Colombia was evaluated on Artemia salina, the results exposed with the CL_{50} = 119.710 μg/mL, are considered by the authors a low value, which means that the oil has low toxicity (Jaramillo *et al.*, 2007).

Acarycidal activity

The total essential oil obtained from *C. malambo*, and the major components, methyl eugenol and methyl isoeugenol were assayed on Dermatophagoides farina. The results of acarycidal activity show that the oil has a high activity against D. farinae, with an LD_{50} of 262 ppm at 30 minutes of exposition. (Mendoza-Meza *et al.*, 2014).

Investigations of the pharmacological actions of the essential oils of *Croton malambo* plants from Venezuela, showing antibacterial and cytotoxic activity have been released, which are commented below.

Antibacterial activity

The antibacterial activity of *C. malambo* leaf essential oil was assayed in vitro by agar diffusion method against Gram-positive

bacteria (*Staphylococcus aureus* and *Bacillus cereus*), Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa)* and, the yeast *Candida tropicalis.* The effect of the pure oil and diluted oil was also compared to standard concentration antibiotics Amikacine, Norfloxacine, and Nystatine. The results showed that the oil from the leaves had antibacterial activity; especially the activity observed against *P. aeruginosa* is very important, because is a bacterium resistant to many antibiotics. The activity was also important for the fungal strain. The reference antibiotics showed the highest antimicrobial activity against all microorganisms and the pure essential oil was more active in all the bacterium. (Suárez *et al.*, 2008)

Cytotoxic activity

The cytotoxic activity in vitro of *C. malambo* leaf essential oil was evaluated against MCF-7 (human breast cancer), PC-3 (prostate carcinoma), LoVo (colon carcinoma), and normal fibroblast. All the cell lines were submitted to growing concentrations of essential oil (5, 15, 25, 50, 75, 100 μg/mL). The results indicated that the oil was more active against cancer MCF-7 cells with an IC_{50} value of 72.84 %. This anticancer activity showed, suggested a selective effect against the MCF-7, which could be attributed to a synergistic effect of all components in the oil, like other oils from this genus, or maybe due to the high concentration of the principal component, the monoterpene methyl eugenol which showed some interesting biological activity, and because the related monoterpene eugenol had been reported with apoptotic activity on leukemia cells (Suárez *et al.*, 2008).

Conclusions

This review summarizes information regarding the traditional uses and phytochemical and pharmacological investigations of *Croton malambo*. Studies related to identifying the chemical constituents in leaves and barks showed that the main metabolites belonging to the terpenoid compounds are diterpenes with kaurane and neoclerodane structures. The essential oils of leaf and bark are well characterized and shown to be rich in phenylpropanoids like methyl eugenol. The diterpenes isolated from this plant are endowed with many pharmacological activities. The biological activities of extracts and pure compounds are mostly carried out in vitro experiments, however, the studies of antidiabetic, anti-inflammatory, and anticancer activities deserve deeper research on the active constituents of this plant, which evidenced the potential to obtain from its new pharmaceutical to treat these diseases.

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