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Botanical description, ethnomedicinal uses, phytochemistry and pharmacological effects of *Croton dichogamus* Pax (*Euphorbiaceae*)

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ABSTRACT

Croton dichogamus Pax (Euphorbiaceae) has been used widely in traditional ethnopharmacological practices against a wide number of ailments. The pharmacological activities, phytochemical composition and its safety aspects have been covered in a number of articles. The present review aims to provide a comprehensive literature overview regarding botanical description, phytochemical composition, local uses, pharmacology and toxicological effects of crude extracts, fractions and isolated compounds obtained using different solvent systems. The review was compiled through a thorough literature search from authentic resources using Google, Google Scholar, Medline, PubMed, Chemical abstracts, Web of Science, Scopus, Science Direct, peer reviewed articles, books and thesis. *Croton dichogamus* is an important ethnomedicinal plant used traditionally for the treatment of tuberculosis and other respiratory tract infections, stomach ache, fever, sexually transmitted diseases such as syphilis and gonorrhea, impotence, arthritis, tooth ache, infertility and malaria. Pharmacological and toxicological studies performed on the fresh plant parts and crude extracts prepared using different extraction solvents validates the ethnomedicinal utilization of *Croton dichogamus*. Studies performed validate the use of *Croton dichogamus* extracts in antimicrobial, antioxidative and antiproliferative therapy. Information on therapeutic validation in analgesia, hypertension, wound healing, gastrointestinal motility and diabetes mellitus is scanty. To further advance the local use of *Croton dichogamus* in the above-mentioned illnesses, there is an urgent need for further studies to validate the traditionally reported anecdotal efficacy and safety. Data on safety of various crude extracts of *Croton dichogamus* is also scanty. However, the available information on toxicology of *Croton dichogamus* suggests it is safe. The current review supports in part, the ethnomedicinal use of the medicinal plant. However, in-depth studies aimed at efficacy and safety evaluation, in addition to identification of compounds responsible for the reported activities is required. This information will support steps towards discovery of novel ligands with activity against illnesses reported above.

Keywords: *Croton dichogamus* Pax, Botanical description, Phytochemistry, Pharmacology, Toxicology, Traditional medicine.

INTRODUCTION

The medicinal value of plants has been exploited for disease alleviation since time immemorial [1]. The accessibility, availability, effectiveness, and affordability of medicinal remedies make traditional medicine a popular form of treatment [2].*Croton* (Euphorbiaceae) has 1300 species, most of them extensively used in traditional medicine, owing to their ability to treat a broad spectrum of diseases [3, 4]. Some species from this genus have important validated medicinal properties that can provide leads in drug design and development [5]. For instance, the leaves and stem bark extracts of *Croton cajucara* are used in form of pills for the treatment of diabetes, weight loss, high blood cholesterol and gastrointestinal disturbances; the methanolic root extracts of *Croton lobatus* have been reported to have activity against *Plasmodium falciparum* strains, sensitive to Chloroquine [4]. The dichloromethane leaf extract of *Croton zambesicus* showed *in vitro* cytotoxicity against human cervix carcinoma cells; anti-tumor activity was also shown by the red latex of *Croton lechleri* [4]. The methanolic leaf extracts of *C. lechleri* have also shown wound healing activity and an ability to heal gastric ulcers by reducing ulcer size and bacterial content of the ulcer [4]. Moreover, one of the active ingredients of a commercially available anti- ulcer agent Kelnac ™ is from the leaves of *Croton stellapilosus*, a Thai *Croton* species [5].

Croton is perceived to adapt to diverse climatic conditions and different soil types which could be the reason why its numerous species are found in most parts of the globe [6]. Due to its adaptive features, *Croton* genus has evolved at a very high rate, such that within the genus there are *Croton* subgenera like Geiseleria [7]. Its global availability and resilience to harsh climatic conditions has increased its

utilization as an anti-tumor, antidiabetic, antiviral, antispasmodic, antimicrobial, acetylcholinesterase inhibitor, anti-ulcer, anti-inflammatory and neuritic outgrowth-promoting agent [4].

C. dichogamus, one of the species of *Croton* has been reported to grow in Ethiopia, Kenya, Mozambique, Somalia, Rwanda, Madagascar and Tanzania, where it plays a key role in traditional medicine [8]. Phytochemical screening done on numerous crude extracts of the leaves, stem bark and leaves of *C. dichogamus* has reported the presence of secondary metabolites such as alkaloids, flavonoids, tannins, saponins, steroids and numerous terpenoids [9, 5, 10]. The existence of a fair quantity of all these phytochemicals in *C. dichogamus* has qualified it for curative use in traditional medicine as a tonic to improve digestion [11], as an antimalarial, an antipyretic and as a nutritional supplement for milk [11, 12, 19], to treat polio-like symptoms, and chest pain [13], and also to alleviate back pains. It has also been used to alleviate stomachache, chest problems, oedema and cough [14], to manage asthma [15], arthritis and gonorrhea [16]. A study conducted in the mid-1900s in south Baringo district indicated that *C. dichogamus* is a highly nutritive shrub to both animals and humans containing 25.14% protein, 42.30% carbohydrate, 20.08% crude fiber, 1.08% calcium and 0.49% phosphorus [17]**.** Wild herbivores in Africa consume this plant as their main food especially the elephants, giraffes and buffaloes [18]. The current review therefore focuses on traditional uses, phytochemistry, biological activities and toxicologic effects of *C. dichogamus.*

Taxonomic tree

Domain - Eukaryota

Kingdom - Plantae

Phylum - Tracheophyta

Class - Magnoliopsida

Order - Malpighiales

Family - Euphorbiaceae

Genus - *Croton L*.

Specific epithet - dichogamus

Scientific Name - *Croton dichogamus* Pax

Morphology

C. dichogamus is a shrub with regular, repeated branching and a tapered or trailing wreath. The leaves are normally sleeky, tabular covered with silvery scales and the upper side is yellowish brown [8]. The flowers are monecious; each flower has twenty stamens that contain six sepals. This flower doesn't have any petals, its pistils have five sepals, divisions are sleeky and linear, designs are bipartite, the ovary is covered with round tabular scales [19]. *C. dichogamus* grows up to 7.5 meters tall or more but is usually only 2-5 meters. The fruit of *C. dichogamus* is spherical, three-parted, and slightly bigger than a pea [8].

The habitats of *C. dichogamus* may include acacia woodland, bushland, thicket, dry forest, on rocky ground, lava, limestone and porous soils and sometimes forming dense stands at elevations from 550-1800 meters [20].

Figure 1: Photo of *Croton dichogamus* Pax (Euphorbiaceae*)* plant. The picture was taken in Kisumu East, by Dorine Matara and authentication done at East African Herbarium.

Traditional uses

In Tanzania**,** the roots of *C. dichogamus* are milled then mixed with porridge for the treatment of tuberculosis because the shrub is believed to be efficient in the management of respiratory ailments [11]. The leaves are also used as tonic, antimalarial and as a nutritional supplement [11]. The smoke from the burnt leaves *of C. dichogamus* is inhaled by patients to provide relief from fever [11, 21]. The Batemi and Maasai of East Africa add C. *dichogamus* to milk and meat based soups to eliminate cardiovascular diseases caused by high levels of cholesterols [10]. The agro pastoral communities in Mbulu, Tanzania use *C. dichogamus* as a pesticide to control storage pests in groundnuts [22]. They also use it for the treatment of urinary tract infections and tooth-aches [22, 23].

Among the Samburu community in Kenya, C. *dichogamus* is used to alleviate chest pains, and stomach aches [9]. In Loitoktok district in Kenya, the plant is used to manage arthritis and gonorrhea [16]. In Nyanza province, the Luo community use *C.dichogamus* to nurse patients with asthma and other respiratory illnesses [15]. In a plant sanctuary called Mutomo, in Kitui County, *C. dichogamus* stem bark and leaves are made into an infusion that is drunk to alleviate back-pains, malaria, stomachache, chest problems, fever, oedema and cough [14]. A root decoction is also drunk for the treatment of impotence and infertility [14]. In Narok county, the roots of *C. dichogamus* are used to treat polio like symptoms, gonorrhea, and chest pain [13]. The Marakwet community in Kenya ingest the boiled roots, flowers and leaves of *C. dichogamus* to relieve abdominal pain, oral thrush and wheezing. The Ethiopians make a paste out of the roots of *C. dichogamus* for vaginal application to enhance female reproductivity [13].

Botanical description

Traditionally, *C. dichogamus* is referenced using various local names by different communities (Table 1).

Table 1: Local names associated with *C. dichogamus*

Community	Local name
Latin (scientific name)	*Croton dichogamus*
Swahili	Mhande
Dholuo	Rachar
Samburu	L-akirding'ai
Masaai	Enkitaru/Oloiborbenek
Batemi	Msiniya/Mgilalugi
Mbeere	Muthima
Kinyarwanda	Umuhuhe
Marakwet	Kelerwe
Maa	Olokidigai
Afaan Oromo	Maffuka
Dorobo	Localdongai
Girigirumu	Mbulu
Kamba	Mwalula

Phytochemistry

Secondary metabolites in *C. dichogamus* extracts

Phytochemical reports have shown the presence of a numerous metabolites which have been isolated from methanolic, n-hexane, dichloromethane and ethanolic crude extracts of *C. dichogamus* and identified by their spectroscopic data in comparison with available literature [9]. The methanolic root extract of *C.dichogamus* was reported to contain terpenoids, saponins, tannins, steroids, alkaloids and flavonoids [9, 10]]. An ethanolic crude root extract from *C. dichogamus* indicated the presence of terpenoids and steroids [24]. The ethanolic leaf extract has been reported to contain flavonoids, saponins and tannins while the ethanolic stem extract has been reported to have a moderate distribution of terpenoids, saponins, tannins, steroids and alkaloids [24]. There is no phytochemical analysis performed on the fruits and flowers from *C. dichogamus*. The distribution of the compounds in various parts of C. *dichogamus* is represented below (Table 2).

Table 2: Secondary phytochemical metabolites identified from *Croton dichogamus*

Phytochemical component	Level of phytochemicals in different plant parts		
	Roots	Stems	Leaves
Terpenoids	+++	++	+
Saponins	++	++	++
Flavonoids	+	++	+++
steroids	+	+	+
Tannins	++	++	++
alkaloids	+	+	+

Key: Lowly present +, Moderately present ++, Highly present +++.

Quantitative phytochemical analysis and isolated compounds

Phytochemical analysis on the ethanolic root extract of *C.dichogamus* indicated that the terpenoids were higher in yield that the other compounds investigated, such as phenols, tannins, alkaloids, saponins and steroids [24]. The methanolic root extract of *C.dichogamus* was reported to be rich in terpenoids, saponins and tannins [10], while steroids, alkaloids and flavonoids were also present in minimal amounts [9, 10]. The ethanolic leaf extract was reported to contain a higher concentration of flavonoids, saponins and tannins while the ethanolic stem extract has been reported to have a moderate distribution of terpenoids, saponins, tannins, steroids and alkaloids [24]. Aldhaher *et al.,* [9] reported that a root extract of *C. dichogamus* contain 6.8 and 5.1 mg/g dry weight of total phenolic and tannin content respectively. Chapman *et al.,* [25], reported considerable amounts of saponins in froth assays and hemolytic assays of n-butanoic crude extract from C. *dichogamus* which were experimentally observed to be devoid of hemolytic crisis that is associated with saponins. Due to the existence of a higher concentration of terpenoids in *C. dichogamus* in comparison to the other compounds, studies have greatly focused on their quantities and curative effects [5, 9].

Phytochemical screening on n-hexane root extract of *C.dichogamus* has indicated that there are more than 20 types of terpenoids that possess incredible pharmacological activities [9, 5]. These diterpenoids belong to the clerodane, crotofolane, neoclerodane and halimane skeletal types [3, 4]. Crude n-hexane and methanolic extracts of *C. dichogamus* yielded 15 terpenoids; four sesquiterpenoids, one enantiomer of a known sesquiterpenoid, four Ent-clerodane diterpenoid, two Ent-halimane diterpenoids, three crotofolane diterpenoids and one triterpenoid as indicated below (Table 3).

Table 3: The main diterpenoids in the n-hexane crude root extract of C. *dichogamus* [9, 3]

Chemical name	Category of terpenoid	Molecular formular	Physical description	Percentage occurrence	Mass spectrum
4-patchoulene	sesquiterpenoids	C15H240	White oil	0.026	204.1878
Patchoulene-3-one	sesquiterpenoid	C15H22O	White oil	0.009	218.1671
Cadin1(6),2,4,7,9 penta-ene	sesquiterpenoid	C15H18O	White oil	0.036	198.1409
1(6),7,9-cadinatriene-4α.5β diol	sesquiterpenoid	C15H22O2	White oil	0.015	234.1620
1,3,5-cadinattriene-7R,10s-diol	Enantiomer of a sesquiterpenoid	C15H22O2-H	Yellow oil	0.008	233.1550
15,16-epoxy-13(16),14-ent-clerodadien-3-on	Ent-clerodane diterpenoid	C20H30O2	Yellow oil	0.038	302.2246
15,16-epoxy-4(18),13(16),14-entclerodatrien-3-ol	Ent-Clerodane diterpenoid	C20H30O2	White oil	0.008	302.2246

15,16-epoxy-3-keto-3(16),14-ent clerodadien-17,12S-olide.	Ent -clerodane diterpenoid	C20H26O4	Yellow oil	0.051	330.1831
15,16-epoxy-3,4 dihydroxy-3(16),14-ent-clerodadien-17,12S-olide	Ent -clerodane diterpenoid	C20H28O5	Yellow oil	0.077	371.1831
15,16-epoxy-5,13(16),14-ent-halimatriene-3-ol	Halimane diterpenoid	C20H30O2	Yellow oil	0.009	325.2138
15,16-epoxy-3-hydroxy-5(10),13(16),14-ent-halimatriene-17,12S-olide	Halimane diterpenoid	C20H26O4	White solid	0.016	330.1830
Crotohaumonoxide	Crotofolane diterpenoid	C22H26O2	Yellow oil	0.021	370.1780
Crotodichogamoin A	Crotofolane diterpenoid	C20 H22O4	Yellow gum	0.1	327.1590
Crotodichogamoin B	Crotofolane diterpenoid	C20H2202	Yellow oil	0.015	295.1695
Acetyl aleuritic acid	triterpenoid	C32H50O4	White crystal	0.017	497.3829

Crotodichogamoin B was shown to be an important biosynthetic intermediate of the crotofolane class (Crotohaumonoxide, Crotodichogamoin A and Crotodichogamoin B) [4]. A recent study has reported that a methanolic root extract of *C.dichogamus* yielded five other diterpenoids that are not included in the table above namely depressin, a Caspian diterpenoid, crothalimene A&B and crotocascarin A & B [9]. It was believed that the roots of *C.dichogamus* were the richest source of terpenoids, however an investigation on the ethanolic crude extract from the leaves of *C. dichogamus* has reported two other crotofolane diterpenoids which have not been observed in the methanolic and ethanolic root extracts, namely crotoxide A and crotoxide B [5].

Pharmacological activity

Antimicrobial activity

Antibacterial activity

Pharmacological studies have confirmed that *C. dichogamus* exhibit notable antibacterial properties [19]. The phytochemical components isolated from the plant have demonstrated mild to moderate activity against microbes of bacterial origin [4]. The ethanolic root extract of *C. dichogamus* were reported to have moderate anti-bacterial activity against two Mycobacterium species namely *Indicus pranii* and *Mycobacterium madagascariense indicus*, giving a Minimum Inhibitory Concentration (MIC) values of 1.25 mg/ml [24]. Methanolic root extracts of five other Croton species namely *Croton zambesicus, Croton megalobotrys, Croton macrostchyus, Croton sylvatica, Croton urucurana and Croton trillium* have been reported to inhibit both gram positive and gram negative bacteria especially *Escherichia coli*, *Staphylococcus aureus*, *Bacillus cereus*, *Bacillus subtills* and *Pseudomonas aeruginosa* [6].

Pharmacological screening on a number of the organic extracts from *C. dichogamus* for anti-bacterial activity was consistent with studies done previously [27]. The ant-bacterial activity of the ethanolic root extract of C.dichogamus against *M. madagascariense indicus* and *Indicus pranii* was associated with a fair concentration of triterpenoids and alkaloids [24]. The antimicrobial property of *C. dichogamus* is linked to the very high concentration of terpenoids [24]. The methanolic root extracts which possessed the highest concentration of diterpenoids reported a considerably higher bacterial inhibition than the ethanolic extracts from stems and leaves [6].

Antimalarial activity

The essential oils obtained by steam distillation of the aerial parts of C. *dichogamus* [33], have demonstrated antimalarial or anti-plasmodial activity against *Anopheles gambie* and as a result, the extracts are extensively used against lake basin malaria [26].

Antifungal activity.

Even though the antifungal activity of *C. dichogamus* has never been investigated, some other *Croton* species in South America and Africa inhibited the growth of fungal organisms [4]. The methanolic root extract obtained from *Croton urucurana* hindered the growth of *Trichophyton mentagrophytes* and *Trichophyton tonsurans* [4]. The volatile oil of *Croton cajucara* also showed activity against *Candida albicans* [28].

The presence of catechins like gallocatechin and epigallocatechin in *Croton* species as demonstrated by phytochemical analysis has been noted to influence their antifungal activity [4]. However, pharmacological studies need to be staged to confirm the presence of the antifungal activity in *C. dichogamus*.

Antioxidant activity

There is an exciting free radical scavenging activity in Croton species [28]. Ferric thiocyanate (FTC) and DPPH (2,2- diphenyl-1-picryl-hydrazylhydrate) assays have confirmed the claim that *Croton* species have strong antioxidant activity [29, 4, 28]. Johns *et al.*, [10], indicated that the essential oils obtained from the leaves of *C. dichogamus* contain polyphenols like tannins and flavonoids which exerted significant antioxidant activity. Studies have also indicated that flavonoids in the methanolic stem extract of *C.dichogamus* increased production of antioxidative enzymes which promoted intracellular defense against free radicals [30, 28]. Ethanolic leaf extracts of *Croton cudatum* have shown strong hydrogen peroxide, superoxide and hydrochlorous acid free radical scavenging activity as well as antioxidative potential for chain breaking inhibition of lipid peroxidation. The antioxidation activity has been associated with the presence of flavonoids, cyanogenetic glycoside alkaloids and phenolic compounds [29].

Anti-proliferative activity

Compounds from *C. dichogamus* have shown a modest antitumor activity [9, 5]. For example 10-epi- Maninsgin D, a diterpenoid isolated from the n-hexane and methanolic crude root extracts of *C. dichogamus* when screened *in vitro* for cell viability against CACO (human colorectal adenocarcinoma) cell lines using red assay reduced CACO at 100mM showing significant inhibition of cellular proliferation [9]. The results from a study done later confirmed that another sesquiterpenoid known as furocrotinsulolide isolated from the methanolic root extract of *C. dichogamus* recorded a modest anticancer activity at 30µm when tested on CACO-2 cell line [5].

A fair composition of both diterpenoids and triterpenoids in *C. dichogamus* is believed to be the source of the antiproliferative activity [31]. *Croton cajucara and Croton mubago* which have a fair concentration of sesquiterpenoids in their ethanolic leaf extracts were reported to be active against melanoma(MALME-3M) and renal (UO-31) cell line [31].

Hypocholesteremic activity

Ethanolic stem extracts of *C. dichogamus* were seen to contain phytosterols like b-sitosterol that lower the serum cholesterol levels in humans and animals by preventing the endogenous and exogenous cholesterol absorption [32]. The methanolic stem extract of *C. dichogamus* was reported to contain saponins with an amphiphilic structure that bind with dietary cholesterol and with bile acids to prevent cholesterol absorption [10]. Hypolipidemic outcome was observed in assay with trans dehydrocrotonin from one *Croton* species, *C. cajucara* [4]. Pharmacological studies have also linked the hypocholesteremia activity to *Croton* species to the presence of clerodane diterpenoids, acetyl aleuritolic acid [4], saponins and polyphenols [32]. This has substantiated the folkloric use of *C.dichogamus* in the management of atherosclerosis and coronary heart disease [10]. Polyphenols such as flavonoids and tannins from the methanolic leaf and stem extract of *C.dichogamus* have also been reported to lower cholesterol levels through antioxidation [10].

Insecticidal activity

The crude powdered leaf extract of *C. dichogamus* was highly effective in protecting the Bambara groundnut seeds against damage by field pests and storage insects like *Callosobruchus maculatus* over a period of 180 days [22]. Moreover, the leaf powdered extract indicated great effectiveness against oviposition of bruchids such as *Callosobruchus maculatus* on the Bambara groundnut seeds with eggs on the surface with no toxic effects the herbivores [22].

The diterpene fraction from the methanolic leaf extract of *C. dichogamus* is the source of the insecticidal activity [4], The diterpene moiety from *Croton linearis, Croton aromaticus and Croton californicus* demonstrated significant insecticidal activity [4].

Anti-inflammatory activity

Anti-inflammatory activity has been observed in most of the *Croton* species [3, 4]. Furocrotinsulide A, a compound isolated from the n-hexane leaf and stem extract of *C. dichogamus* and *Croton Poomae* demonstrated significant anti-inflammatory activity by inhibiting nitric oxide production better than standard drugs, indomethacin and dexamethasone [36, 19]. Bioassay -guided fractionation of the aerial parts of *Croton cilitoglandulifer* led to the isolation of tigliane diterpenoids which inhibited the enzyme cyclooxygenase-1(COX-1) and cyclooxygenase-2(COX-2) [34]. A tigane diterpenoid isolated from the branches and leaves of *Croton tiglium* displayed moderate inhibition of enzymes COX-1 and COX-2 [35] and crotonkinin A, a diterpenoid isolated from *Croton tonkinesis* also showed anti-inflammatory activity [4].

Recent studies have reported that the methanolic, n-hexane, ethanolic root and leaf extracts of *C.dichogamus* contained clerodane and sesquiterpenoid diterpenoids which exhibited significant anti-inflammatory activity [36].

Tonic activity

The word tonic refers to medicinal substances that are used to restore the general body health and function of various body organs. Studies have confirmed the folklore claim of *C. dichogamus* being effective as a tonic. Oliver [38], reported that aqueous leaf extracts from C. *dichogamus* contained uterotonic, aphrodisiac, muscle tonic, stomach tonic and muscle tonic activities. The crude extracts from the stem of *C. dichogamus* were also reported to have tonic effects [10].

Toxicology of *C. dichogamus*

C. dichogamus was tested for cytotoxicity using brine shrimp lethality assay. The ethanolic root extract, though toxic, was safer to Brine shrimp larvae with LC_{50} value of 40.70 µg/ml compared to cyclophosphamide, a standard anticancer drug that had LC_{50} value of 16.3µg/ml [24]. Maninsgnin D a compound isolated from the methanolic root extract of *C. dichogamus* was assayed for its cytotoxicity against HL-60, SMMCC-7721, A-549, MCF-7 and SW-480 human tumor cell lines by the MTT which gave an LC_{50} value of less than 40µm [37], indicating that the molecule is potentially toxic. This points towards a high lethality of *C. dichogamus* extracts, calling for dose adjustments in herbal formulations, and further in vivo studies to ascertain the safety of the medicinal plant.

CONCLUSION

A comprehensive literature overview has disclosed that *C. dichogamus* is an essential plant in ethnomedicine for the management of malaria, tuberculosis, asthma, cough, fever, impotence, stomach and tooth aches, chest and back pains, gonorrhea and syphilis. Organic and inorganic crude extracts from various plant parts of *C. dichogamus* have substantiated the folkloric use of the plant. Pharmacological studies have mainly focused on the assessment of the antimicrobial, antiproliferative, hypocholesteremic and pesticidal activity of the plant. A number of studies have evaluated the phytochemical composition of the plant parts using polar and non-polar solvents and various phytoconstituents have been isolated and identified. Despite the extensive use of *C. dichogamus* in traditional medicine, there is minimal scientific literature on its pharmacology and safety. There is a necessity of experimental evidence on antifungal, antipyretic, analgesic, antitussive and antispasmodic properties to validate the traditional use of *C. dichogamus*. There is scanty information appearing on the toxicological profile of *C. dichogamus*. This calls for further studies considering its wide utilization in folkloric medicine. Hence, there is an urgent need for further validation of anecdotal safety and efficacy of *C. dichogamus*, going forward.

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