A Review of Phytochemistry and Pharmacological Properties of Threatened *Croton* Species Used as Herbal Medicines in East Africa

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Abstract: Some rare and threatened *Croton* species have a long history of medicinal usage in East Africa. The objective of this study was to review the phytochemistry and pharmacological properties of five *Croton* species that are threatened with extinction in East Africa but widely used as herbal medicines in the region. Information on medicinal uses, phytochemistry and pharmacological properties of *C. alienus, C. dictyophlebodes, C. jatrophoides, C. megalocarpoides* and *C. talaeporos* was obtained from databases such as Scopus, Web of Science, Science Direct, Google Scholar, PubMed, BioMed Central (BMC), Springerlink and Scielo. Other sources of information included scientific publications, conference proceedings, theses, books and book chapters obtained from libraries. Literature search revealed that the bark, fruits, leaves and roots of these five *Croton* species are commonly used as traditional medicines for gastro-intestinal disorders, colds and influenza, body pains and weaknesses and intestinal worms. Phytochemical compounds isolated from these species include alkaloids, anthraquinones, diterpenoids, esters, flavonoids, furanoditerpenoids, limonoids, methylcyclohexanes, phenolics, steroids, tannins and triterpenoids. Pharmacological studies indicate that these species have antifungal, anti-leishmanial and insect antifeedant activities. Preliminary phytochemical and pharmacological research done so far on *Croton* species is promising, but too general to corroborate some of the medicinal uses of the species.

Keywords: *Croton alienus*, *Croton dictyophlebodes*, *Croton jatrophoides*, *Croton megalocarpoides*, *Croton talaeporos*.

INTRODUCTION

Some rare and threatened plant species are known to have unique chemical compounds characterized by potent biological activities. The genus *Warburgia* Engl. is a typical example [1-5], with most of its species having long history of ethnomedicinal uses in east, central and southern Africa. Due to the popularity of *Warburgia* species as sources of ethnomedicines, most species of the genus are severely over-harvested throughout their distributional ranges. It is within this context that a review of phytochemistry and pharmacological properties of five *Croton* L. species that are threatened with extinction in East Africa but widely used as herbal medicines in the region was carried out. Genus *Croton* is a member of the Euphorbiaceae or spurge family. Presence of biologically active natural products in some members of the Euphorbiaceae family contributed to many members of the family being widely used as herbal medicines in Africa, Asia and South America [6]. Some medicinal applications of *Croton* species include their use in the treatment of cancer, constipation, diabetes, digestive problems, dysentery, external wounds, fever, hypercholesterolemia, hypertension, inflammation, intestinal worms, malaria, pain, ulcers and weight-loss [6]. At least 15 *Croton* species are used as herbal medicines in East Africa [7-16], and among these are five species that are threatened or are of conservation concern (Table **1**).

Croton alienus Pax is a shrub or small tree restricted to humid areas of upland evergreen or secondary forest in central Kenya [17,18]. *Croton dictyophlebodes* A. R.-Sm. is a deciduous medium-sized to large tree up to 20 metres tall restricted to the West Usambara Mountains and montane dry evergreen forest in Tanzania [11,17]. *Croton jatrophoides* Pax is a monoecious or dioecious tree up to 18 m tall recorded in forest edges and clearings, riverine and dry coastal forest in Tanzania [11,17], but also said to occur in south-east Kenya and Central African Republic [13]. *Croton megalocarpoides* Friis & M. G. Gilbert is a monoecious shrub to small tree growing up to 8 m tall recorded in semi-evergreen coastal forests, bushland and mountainous areas in Kenya, Mozambique, Somalia, Tanzania [17,19]. *Croton talaeporos* A. R.-Sm. is a monoecious or sometimes dioecious many-stemmed small or large tree up to 10 m tall recorded in coastal bushland and wooded grassland in Kenya and southern Somalia[17]. The present review is aimed at documenting the

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ISSN: 2223-3806 / E-ISSN: 1927-5951/18

Table 1: *Croton* Species in East Africa that are Threatened or are of Conservation Concern

Croton species	IUCN status	Distribution	Conservation concerns and threats	References
C. alienus	Endangered (Bl+2c)	Kenya	Habitat transformation and loss result in small and relatively isolated subpopulations. Species population is negatively affected as its habitat is converted to agricultural land and human settlement. As an endemic species characterized by extreme fluctuations in extent of occurrence and area of occupancy, over-collection will pause a major threat to the species.	[18,20]
C. dictyophlebodes	Vulnerable (Bl+2b)	Tanzania	The species population is continuing to decline due to habitat transformation and loss. Population size negatively affected by decreasing area, extent and/or quality of habitat and decreasing number of mature individuals.	[20]
C. jatrophoides	Vulnerable (Bl+2b)	Kenya, Tanzania	Just like *C. dictyophlebodes*, the species population is continuing to decline due to habitat transformation and loss. Population size negatively affected by decreasing area, extent and/or quality of habitat and decreasing number of mature individuals.	[20]
C. megalocarpoides	Near threatened	Kenya, Mozambique, Somalia, Tanzania	Evaluations carried out in Kenya and Tanzania indicate that the species is likely to become at risk of extinction in the near future.	[18,20]
C. talaeporos	Near threatened	Kenya, Somalia	*Croton talaeporos* is naturally rare in Somalia, and therefore, the species is likely to become at risk of extinction in the near future.	[20]

ethnomedicinal uses, phytochemistry and pharmacological properties of five *Croton* species that are threatened with extinction in East Africa. Results of this study are expected to reveal research challenges and perspectives required to address the dilemma associated with popular herbal medicines that are threatened due to anthropogenic activities in the tropics. I hope that this information will highlight the importance of the genus and will provide baseline information for future researchers intending to do further work on genus *Croton*.

MATERIALS AND METHODS

The following five Croton species, C. alienus (Mildbraedia balboana Chiov.), C. dictyophlebodes, C. jatrophoides, C. megalocarpoides and C. talaeporos (C. integrifoliussensu T.S.K.) were used as the keywords in searching the major databases including Web of Science, Scopus, Google Scholar, Science Direct, BioMed Central (BMC), PubMed, Scielo and Springerlink documenting their ethnomedicinal uses, ethnobotany, ethnopharmacology, pharmacology, phytochemistry and therapeutic value of the species. Additional literature, including pre-electronic literature such as dissertations, theses, international journal articles, scientific reports from international, regional and national organizations, conference papers and books were sourced from the University of Fort Hare library in South Africa. This review draws heavily on the research results published in international journals (25), books (six), book chapters (two), dissertations and theses (two) and conference proceedings (two).

Ethnomedicinal Uses

A total of 14 human diseases and ailments are treated with herbal concoctions prepared from Croton species (Table **2**). Gastro-intestinal disorders (stomachache and stomach complaints), colds and influenza, body pains and weaknesses, and intestinal worms are the most commonly treated human diseases (Figure **1**). According to Gachathi [12], *C. alienus*is used as herbal medicine for general body weaknesses in Kenya. Fruit infusions and decoctions of *C. dictyophlebodes* are taken orally as remedy for intestinal worms in Tanzania [11]. *Croton jatrophoides*is used as herbal medicine for fever, headache and influenza in Kenya [12]. In Tanzania, fruit and root infusions and decoctions of *C. jatrophoides* are taken orally as remedies for colds, intestinal worms and stomachache [7,11,21]. Ethnobotanical research by Kiringe [10] revealed that *C. megalocarpoides* is used as herbal medicine in Kenya to induce vomiting, induce bile release if one is suspected to have malaria and as remedy for stomachache. In Kenya, leaf and root infusions of *C. talaeporos*are used as remedies for body pains, body swellings, colds, inflammation and stomach complaints [8,9,13] and seeds are used as a laxative in Somalia [22].

Table 2: Ethnomedicinal uses of *Croton* Species that are Threatened with Extinction in East Africa

Use	Plant parts used	Country practiced	References
C. alienus			
Body weaknesses	Not specified	Kenya	[12,15]
C. dictyophlebodes			
Intestinal worms	Fruit decoction or infusion taken orally	Tanzania	[11]
C. jatrophoides			
Colds	Root decoction and infusion taken orally	Tanzania	[7,11,21]
Fever	Not specified	Kenya	[7]
Headache	Not specified	Kenya	[7]
Influenza	Not specified	Kenya	[7]
Intestinal worms	Fruit and root decoction or infusion taken orally	Tanzania	[7,11,21]
Stomachache	Root decoction and infusion taken orally	Tanzania	[7,11,21]
C. megalocarpoides			
Induce vomiting	Not specified	Kenya	[10]
Induce bile release	Not specified	Kenya	[10]
Stomachache	Not specified	Kenya	[10]
C. talaeporos			
Body pains	Leaf and root infusions	Kenya	[9]
Body swellings	Leaf and root infusion applied on affected body part	Kenya	[8]
Colds	Root infusion taken orally	Kenya	[13]
Inflammation	Leaf and root infusion applied on affected body part	Kenya	[9]
Laxative	Seed infusion taken orally	Somalia	[22]
Stomach complaints	Root infusion taken orally	Kenya	[13]

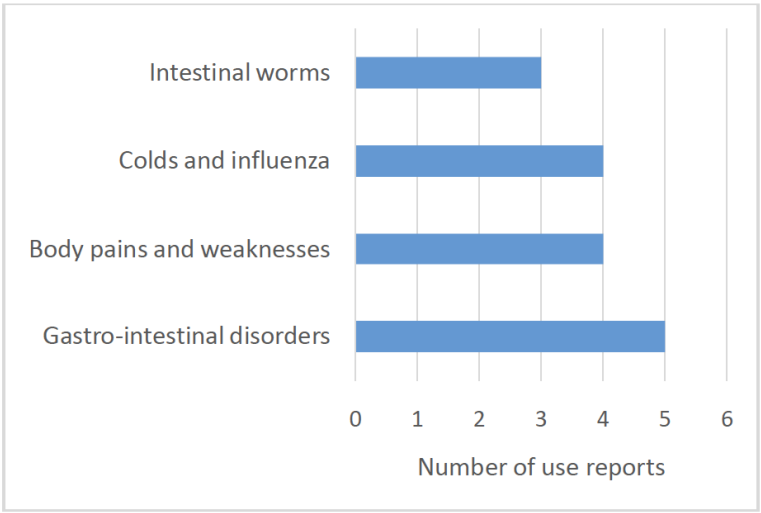

Figure 1: Medicinal uses of threatened *Croton* species in East Africa.

Phytochemistry and Pharmacological Activities

These five *Croton* species have high pharmaceutical value due to alkaloids [14,15], diterpenoids [14,16], esters [14,15], furanoditerpenoids [23,24], limonoids [25-29], methylcyclohexane [14,15,30], steroids [15] and triterpenoids [14,15] that have been isolated from bark, leaves and roots.

Chhabra *et al*. [30] isolated crotepoxide, methylcyclohexane from a stem bark of *C. alienus* (Table **3**). Ndunda [14] and Ndunda *et al*. [15] isolated methylcyclohexane, pentacyclic triterpenoid, ester, alkaloid and steroid compounds, namely crotepoxide, dideacetylcrotepoxide, monodeacetylcrotepoxide, α-senepoxide, β-senepoxide, (+)-(2*S*, 3R)-diacetoxy-1-benzoyloxymethylenecyclohex-4, 6-diene, acetyl aleuritolic, alienusolin, benzyl benzoate, crotonimide C, julocrotine and 24-ethylcholesta-4,22-dien-3-one24-ethylcholesta-4,22-dien-3-one24-ethylcholesta-4,22-dien-3-one from leaves and roots of *C. alienus* (Table **3**). Limonoids, namely dumsin, zumsin, zumketol, zumsenin, zumsenol, dumnin, dumsenin, musidunin and musiduol were isolated from root bark of *C. jatrophoides* [25-29] (Table **3**). Mbwambo *et al*. [23] and Magadula *et al*. [24] isolated four furano diterpenoids namely, isoteucvin, jatropholdin, penduliflaworosin and teucvin from roots of *C. jatrophoides* (Table **3**). Ndunda [14] and Ndunda *et al*. [16] isolated triterpenoids, abietane, ent-clerodane and trachylobane diterpenoids, namely acetylaleuritolic acid, lupeol, isolophanthin A, isolophanthin E, abietic acid, crotocorylifuran, 12-epi-crotocorylifuran, 8β-hydroxycrotocorylifuran, crotocorylifuran-2-one, 7, 8-dehydrocrotocorylifuran, megalocarpoidolide A, megalocarpoidolide B, megalocarpoidolide C, megalocarpoidolide D, megalocarpoidolide E, megalocarpoidolide F, megalocarpoidolide G, megalocarpoidolide H, 3α, 18-dihydroxytrachylobane, ent-trachyloban-18-ol, ent-trachyloban-18-oic acid and ent-3α-hydroxytrachyloban-18-al (Table **3**).

Phytochemical screening of the aqueous and methanol extracts of *C. alienus* and *C. megalocarpoides* showed trace elements of

Table 3: Phytochemical Compounds Isolated from *Croton* Species that are Threatened with Extinction in East Africa

Compound	Plant parts used	References
C. alienus		
Methylcyclohexanes		
Crotepoxide	Leaves, roots, stem bark	[14,15,30]
Dideacetylcrotepoxide, monodeacetylcrotepoxide, α-senepoxide, β-senepoxide, (+)-(2*S*, 3R)-diacetoxy-1-benzoyloxymethylenecyclohex-4, 6-diene	Leaves, roots	[14,15]
Triterpenoid		
Acetyl aleuritolic	Leaves, root	[14,15]
Esters		
Alienusolin, benzyl benzoate	Leaves, root	[14,15]
Alkaloids		
Crotonimide C, julocrotine	Leaves, root	[14,15]
Steroid		
24-ethylcholesta-4,22-dien-3-one	Leaves, root	[15]
C. jatrophoides		
Limonoids		
Dumsin, zumsin, zumketol, zumsenin, zumsenol, dumnin, dumsenin, musidunin and musiduol	Root bark	[25-29]
Furano diterpenoids		
Isoteucvin, jatropholdin, penduliflaworosin, teucvin	Root	[23,24]
C. megalocarpoides		
Triterpenoids		
Acetylaleuritolic acid, lupeol	Roots	[14,16]
Abietane diterpenoids		
Isolophanthin A, isolophanthin E, abietic acid	Roots	[14,16]
Ent-clerodane diterpenoids		
Crotocorylifuran, 12-epi-crotocorylifuran, 8β-hydroxycrotocorylifuran, crotocorylifuran-2-one, 7, 8-dehydrocrotocorylifuran, megalocarpoidolide A, megalocarpoidolide B, megalocarpoidolide C, megalocarpoidolide D, megalocarpoidolide E, megalocarpoidolide F, megalocarpoidolide G, megalocarpoidolide H	Roots	[14,16]
Trachylobane diterpenoids		
3α, 18-dihydroxytrachylobane, ent-trachyloban-18-ol, ent-trachyloban-18-oic acid, ent-3α-hydroxytrachyloban-18-al	Roots	[14,16]

anthraquinones, tannins, phenolics and flavonoid [14]. The methanol extracts of the stem barks of *C. megalocarpoides* were found to have very low total phenolic content (TPC; 1.89 + 0.02% - 1.14 + 0.01% w/w equivalent of gallic acid). These extracts were additionally found to have low antioxidant potential with half maximal inhibitory concentration (IC_{50}) value which was > 1000 µg / ml and ascorbic acid exhibited IC_{50}value of 9.51 µg/ml [14]. The same author also evaluated antifungal activities of aqueous and methanol root extracts of *C. alienus* against *Aspergillus niger, Cryptococcus neoformans* and *Candida albicans* with nystatin and dimethyl sulfoxide (DMSO) as positive and negative controls, respectively. The root and stem bark aqueous extracts of *C. alienus* were active towards *C. albicans* at the lowest concentration of 25 mg/mL tested [14]. The compound ent-trachyloban-19-oic acid has been found to have antimicrobial activity against methicillin resistant *Staphylococcus aureus* and *Mycobacterium smegmatis* [31]. Both ent-trachyloban-19-oic acid and its derivative, ent-trachyloban-19-oic methyl ester inhibited the growth of *Streptococcus mutans* (associated with caries) at 8.9 and 70.5 µg/mL respectively and had biofilm formation by the same bacteria at 32.5 and 125.0 µg/mL respectively [32]. These findings somehow corroborate the traditional use of *Croton* species as herbal medicine against fungal infections.

Ndunda [14] evaluated *in vitro* anti-leishmanial activities of *C. alienus* bark, leaf and root extracts using alamar blue assay by testing growth of *Leishmania donovani* promastigotes with pentamidine and amphotericin B as positive controls. The methanol:dichloromethane (1:1) leaf extract showed activity against *Leishmania donovani* with IC_{50} value of 80µg/mL [14]. Compound crotepoxide isolated from *Croton macrostachyus* Hochst. & Delile demonstrated ant-leishmanial activities against promatigotes and amastogotes of *Leishmania aethiopica* which were comparable to reference ant-leishmanial drugs, amphotericin B and mittefosine [33]. Compound aleuritolic acid isolated from *Discoglypremma caloneura* (Pax) Prain (family Euphorbiaceae) exhibited significant anthelminthic activities on the vitality of adult male worms of *Onchocera gutturosa* [34]. Although none of the *Croton* species documented in this study is used against visceral leishmaniasis, research by Tajebe *et al*. [35] showed that visceral leishmaniasis patients are often co-infected with intestinal parasites. Research conducted by Kokwaro [7], Lovett *et al*. [11] and Watt and Breyer-Brandwijk [21] showed that *C. dictyophlebodes* and *C. jatrophoides* are widely used in Tanzania as herbal medicines against intestinal worms.

Nihei *et al*. [26-29] evaluated insect antifeedant activities of compounds dumnin, dumsenin, musidunin, musiduol, zumketol and zumsinisolated from *C. jatrophoides* using leaf disk assay and second-instar larvae of *Pectinophora gossypiella* and *Spodoptera frugiperda* as test organisms. The two compounds showed antifeedant activities with 50% protective concentration (PC_{50}), PC_{90} and PC_{95} values ranging from 0.5 µg/mL to 36 µg/mL against the larvae of *Pectinophora gossypiella* and *Spodoptera frugiperda* [26-29]. Similarly, Kinyoda *et al*. [36] evaluated antifungal activities of hexane, ethyl acetate and methanol root, bark and leaf extracts of *C. jatrophoides* against *Fusarium oxysporum* f. sp. *lycopersici* using disc diffusion assay. *Fusarium oxysporum* f. sp. *lycopersici* causes soil borne disease in tomatoes (*Solanum lycopersicum* L.) both in the field and greenhouses. The extracts exhibited some activities with growth inhibition zones ranging from 4.17 mm to 8.61 mm and all extracts exhibiting the minimum inhibition concentration (MIC) of 50 mg/ml [36].Further studies are required to establish mechanisms of control against *Fusarium oxysporum* f. sp. *lycopersici, Pectinophora gossypiella* and *Spodoptera frugiperda*, as *C. jatrophoides* can provide an effective control option where synthetic products are unavailable or unaffordable particularly in remote rural areas in East Africa.

CONCLUSION

The present study summarizes ethnomedicinal uses, phytochemistry and pharmacological properties of the five *Croton* species that are threatened with extinction in East Africa. There are similarities and overlaps in terms of ethnomedicinal uses, phytochemistry and pharmacological properties. Future studies should try to establish whether there are phytochemical compounds and pharmacological properties that could be used to distinguish these species. The contemporary research involving *Croton* species is promising, but it is too preliminary and sometimes too general to be used to explain and support some of the ethnomedicinal uses of the species. For example, *C. alienus, C. jatrophoides* and *C. talaeporos* are used as remedies for pain and inflammation, therefore, there is need for detailed anti-inflammatory and analgesic activities of both crude extracts and compounds of the species. Future studies should also focus on toxicity and safety evaluation of the crude extracts and chemical compounds isolated from the species. Detailed *in vitro* and *in vivo* genotoxic studies of these species is required to confirm the

ethnomedicinal and pharmaceutical value of the species.

ACKNOWLEDGMENTS

The author would like to express his gratitude to the National Research Foundation, South Africa (NRF) and Govan Mbeki Research and Development Centre (GMRDC), University of Fort Hare for financial support to conduct this study.

CONFLICT OF INTEREST

No conflict of interest is associated with this work.

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Received on 31-08-2018 Accepted on 03-09-2018 Published on 23-10-2018

DOI: https://doi.org/10.29169/1927-5951.2018.08.04.5