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Review Article

Croton species in Madagascar: their ethnomedicinal uses, phytochemistry and biological activities

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Abstract

Croton species collected from the wild have always been used as herbal medicines for various diseases in Madagascar. The objective of this investigation was to review the ethnomedicinal uses, phytochemistry and biological activities of *Croton* species that are endemic to Madagascar. Relevant literature search was carried out using internet sources such as ACS, Web of Science, Wiley, SpringerLink, Scopus, Mendeley, Google Scholar, Pubmed, SciFinder, BioMed Central, Science Direct and Elsevier. Other literature sources were conference papers, book chapters, books, theses and websites. Literature sources revealed that leaves, bark, roots and twigs of *Croton* species are commonly used as traditional remedies for 38 human diseases and ailments in Madagascar. Cough, malaria, stomach problems, hypertension, asthma, colic and fever are the most commonly treated human diseases, including use of leafy branches of *Croton* species as insect and lice repellents. Phytochemical compounds isolated from *Croton* species include alkaloids, diterpenoids, essential oils, flavonoids, furanoditerpenoids and triterpenoids. Preliminary pharmacological studies indicate that crude extracts and compounds isolated from these species have antimicrobial and cytotoxic activities. In as much as the medicinal potential of *Croton* species should be evaluated, more intensive phytochemical and pharmacological assessments should be conducted to enhance the pharmaceutical potential of the species.

Keywords: Croton, Endemic species, Madagascar, Phytochemistry, Pharmacological properties

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Introduction

The genus *Croton* L. is second to genus *Euphorbia* L. in terms of number of species in the Euphorbiaceae or spurge family, with the number of species estimated to be 1200 (Van Ee et al., 2011) of trees, herbs and shrubs, and sometimes lianas which are associated with forest regions in the tropical zone of the world (Berry et al., 2005). About 149 *Croton* species have been recorded in Madagascar alone (Malcolm and Radcliffe-Smith, 2017). Research by Schmelzer and Gurib-Fakim (2008) showed that 40 *Croton* species are used as herbal medicines in Madagascar. Several *Croton* species are used as herbal medicines against intestinal worms, hypertension, diabetes, cancer, digestive problems, external wounds, malaria, gastric

problems, inflammation, fever, pain, ulcers, dysentery, weight-loss, haemorrhoids, constipation and hypercholesterolemia (Salatino et al., 2007; De Lima et al., 2010; Maroyi, 2012a; Maroyi, 2017a,b,c). Research by De Lima et al. (2010) revealed that *Croton* species produce latex which is rich in chemical compounds which include terpenoids, flavonoids, diterpenoids, alkaloids, terpenes and ricin-type toxins characterized by several biological and pharmacological activities. Pharmacological properties of chemical compounds isolated from *Croton* species or plant extracts include hypolipidemic, hypoglycaemic, antioestrogen, anticancer, antihypertensive, antiinflammatory, antispasmodic, antileishmanial, anti-malarial, antiviral, anti-microbial, antinociceptive, antispasmodial, anti-ulcer, cardiovascular, cytotoxic, gastroprotective, myorelaxant and wound healing (Salatino et al., 2007; De Lima et al., 2010).

Significance of *Croton* taxa in traditional, complementary and alternative medicine in Madagascar is well documented. The leafy branches of *C. antanosiensis* Leandri, *C. barorum* Leandri, *C. bernierus* Baill., *C. decaryi* Leandri, *C. greveanus* Baill., *C. humbertii* Leandri, *C. isomonensis* Leandri and *C. nitidulus* Leandri are used as insect and lice repellents in Madagascar (Schmelzer and Gurib-Fakim, 2008). Leaf, root and stem bark infusions and decoctions of *C. ambanivoulensis* Baill., *C. anisatus* Baill., *C. barorum*, *C. boinensis* Leandri, *C. geayi* Leandri and *C. sakamaliensis* Leandri are taken orally as remedies for diarrhoea, dysentery and stomach problems (Schmelzer and Gurib-Fakim, 2008; Radulovic et al., 2006; Ruphin et al., 2016). In fact, several ethnobotanical studies have shown that *Croton* species are widely used in the treatment and management of asthma, cough, fever, gonorrhoea, hypertension, intestinal worms, malaria, pain and rheumatism in Madagascar (Rasoanaivo et al., 1992; Rakotonandrasana et al., 2010; Ruphin et al., 2016). The documented medicinal applications of *Croton* species are linked to presence of aromatic and volatile oil constituents that demonstrated anti-inflammatory, antinociceptive, gastroprotective, antileishmanial, antimicrobial, anti-gastric ulcer, antiparasitic, cardiovascular, antinociceptive, cardiovascular, intestinal myorelaxant and antispasmodic effects (Radulovic et al., 2006; Salatino et al., 2007; De Lima et al., 2010; Rakotonandrasana et al., 2010; Rabehaja et al., 2014; Ruphin et al., 2016). In this study, the ethnopharmacological assessment of *Croton* species in Madagascar was carried out aimed at providing a comprehensive summary of medicinal uses, chemical properties and pharmacological activities of the *Croton* species.

Material and Methods

In this study, the focus was on *Croton* species that are endemic to Madagascar that are widely used as herbal medicines in the country. Therefore, *Croton* species included in this study are characterized by at least two ethnomedicinal uses documented in scientific papers providing information on plant identity, plant parts used and the diseases or ailments. The catalogue of the plants of Madagascar (http://www.tropicos.org/Project/Madagascar), international plant name index (www.ipni.org), Missouri and Royal Botanic Gardens, (USA and UK) plant name database (www.theplantlist.org) were used to check whether the scientific names and plant authorities are valid, and also confirm whether the plant species are endemic to Madagascar or not. Therefore, this study utilized findings of ethnobotanical studies carried out in Madagascar, as well as data collected through publications such as journals, conference proceedings, books and book chapters. The data on medicinal uses, chemical properties and biological activities of *Croton* species was performed from February to December 2017. Sources of information included internet sources such as ACS, Web of Science, Wiley, SpringerLink, Scopus, Mendeley, Google Scholar, Pubmed, SciFinder, BioMed Central, Science Direct and Elsevier. Other literature sources were conference papers, book chapters, books, theses and websites.

Ethnomedicinal uses

Ethnomedicinal uses of *Croton* species are referred to in many folkloric and ethnobotanical studies carried out in Madagascar (Table 1) where the leaves, roots, stem bark and twigs of the species are used as primary sources of traditional medicines. A total of 38 human diseases and ailments are treated with *Croton* species (Table 1). Cough, malaria, stomach problems, hypertension, asthma, colic and fever are the most commonly treated human diseases and ailments, including use of leafy branches of the species as insect and lice repellent (Figure 1).

Table 1: Medicinal uses of *Croton* species in Madagascar

Medicinal use	Plant parts used	References
C. ambanivoulensis Baill.		
Colic	Leaf infusion taken orally	Schmelzer and Gurib-Fakim, 2008
Dysentery	Leaf infusion taken orally	Schmelzer and Gurib-Fakim, 2008
C. anisatus Baill.		
Colic	Leaf infusion taken orally	Schmelzer and Gurib-Fakim, 2008
Dysentery	Leaf infusion taken orally	Schmelzer and Gurib-Fakim, 2008
C. antanosiensis Leandri		
Disinfectant	Leafy branches used as disinfectant	Schmelzer and Gurib-Fakim, 2008
Induce virility	Stem bark used as alcoholic beverage	Schmelzer and Gurib-Fakim, 2008
Insect repellent	Leafy branches used as insect repellent	Schmelzer and Gurib-Fakim, 2008
Lice repellent	Leafy branches used as lice repellent	Schmelzer and Gurib-Fakim, 2008
Ordeal poison	Stem bark decoction taken orally	Schmelzer and Gurib-Fakim, 2008
C. barorum Leandri		
Asthma	Stem and root bark infusion taken orally	Ruphin et al., 2016
Breast cancer	Stem and root bark infusion taken orally	Rakotonandrasana et al., 2010
Cough	Stem and root bark infusion taken orally	Ruphin et al., 2016
Diarrhoea	Stem and root bark decoction taken orally	Schmelzer and Gurib-Fakim, 2008
Fever	Stem and root bark infusion taken orally	Rasoanaivo et al., 1992
Hypertension	Stem and root bark infusion taken orally	Ruphin et al., 2016
Insect repellent	Leafy branches used as insect repellent	Schmelzer and Gurib-Fakim, 2008
Leukemia	Stem and root bark decoction taken orally	Schmelzer and Gurib-Fakim, 2008
Lice repellent	Leafy branches used as lice repellent	Schmelzer and Gurib-Fakim, 2008
Malaria	Stem and root bark infusion taken orally	Ruphin et al., 2016
Stomach problems	Stem and root bark infusion taken orally	Ruphin et al., 2016
C. bernierus Baill.		
Cough	Stem bark infusion taken orally	Schmelzer and Gurib-Fakim, 2008
Insect repellent	Leafy branches used as insect repellent	Schmelzer and Gurib-Fakim, 2008
C. boinensis Leandri		
Rheumatoid arthritis	Infusion of aerial parts taken orally or applied as steam bath	Schmelzer and Gurib-Fakim, 2008
Rheumatism	Infusion of aerial parts taken orally or applied as steam bath	Schmelzer and Gurib-Fakim, 2008
C. catatii Baill.		
Cough	Leaf infusion taken orally	Schmelzer and Gurib-Fakim, 2008
Disinfectant	Root and stem bark used as disinfectant	Schmelzer and Gurib-Fakim, 2008
Dispnea	Leaf infusion taken orally	Schmelzer and Gurib-Fakim, 2008
Euphoria	Bark mixed with *C. noronhae* Baill. And taken as a beverage	Schmelzer and Gurib-Fakim, 2008
Malaria	Root and stem bark taken orally	Schmelzer and Gurib-Fakim, 2008
Stomachache	Leaf infusion taken orally	Schmelzer and Gurib-Fakim, 2008
C. decaryi Leandri		
Insect repellent	Leafy branches used as insect repellent	Schmelzer and Gurib-Fakim, 2008
Lice repellent	Leafy branches used as lice repellent	Schmelzer and Gurib-Fakim, 2008
Psychosis	Aerial parts decoction taken orally	Schmelzer and Gurib-Fakim, 2008
C. geayi Leandri		
Asthma	Decoction of leafy twigs taken orally	Palazzino et al., 1997
Constipation	Decoction of leafy twigs taken orally	Palazzino et al., 1997
Cough	Decoction of leafy twigs taken orally	Ruphin al., 2016
Fever	Decoction of leafy twigs taken orally	Andriamparany et al., 2014
Flu	Root and stem bark infusion taken orally	Andriamparany et al., 2014
Hypertension	Stem and root bark infusion taken orally	Ruphin et al., 2016
Injury	Root and stem bark decoction applied topically	Andriamparany et al., 2014
Malaria	Stem and root bark infusion taken orally	Ruphin et al., 2016

Stomach problems	Stem and root bark infusion taken orally	Ruphin et al., 2016
Swelling	Stem bark and root applied topically	Andriamparany et al., 2014
Wound	Stem bark and root applied on wound	Andriamparany et al., 2014
C. goudotii Baill.		
Aphrodisiac	Stem bark and leaf infusion taken orally	Rakotonandrasana et al., 2010
Blennorrhoea	Leaves and stem bark decoctions applied in bathes and lotions	Rakotonandrasana et al., 2010
Cough	Stem bark and leaves infusion taken orally	Rakotonandrasana et al., 2010
Gonorrhoea	Stem bark and leaves infusion taken orally	Schmelzer and Gurib-Fakim, 2008
Malaria	Stem bark and leaves infusion taken orally	Schmelzer and Gurib-Fakim, 2008
C. greveanus Baill.		
Asthma	Stem and root bark infusion taken orally	Ruphin et al., 2016
Cough	Stem bark infusion taken orally	Ruphin et al., 2016
Gonorrhoea	Aerial parts infusion taken orally	Schmelzer and Gurib-Fakim, 2008
Hypertension	Stem and root bark infusion taken orally	Ruphin et al., 2016
Insect repellent	Leafy branches used as insect repellent	Schmelzer and Gurib-Fakim, 2008
Lice repellent	Leafy branches used as lice repellent	Schmelzer and Gurib-Fakim, 2008
Malaria	Stem and root bark decoction taken orally	Ruphin et al., 2016
Pain	Decoction of aerial shoots taken orally	Schmelzer and Gurib-Fakim, 2008
Stomach problems	Stem and root bark decoction taken orally	Ruphin et al., 2016
C. hovarum Leandri		
Colic	Leaf decoction taken orally	Krebs and Ramiarontosa, 1996
Molluscidal	Aerial parts used against snails	Schmelzer and Gurib-Fakim, 2008
Weakness of the body	Leaf decoction taken orally	Krebs and Ramiarontosa, 1996
C. humbertii Leandri		
Insect repellent	Leafy branches used as insect repellent	Schmelzer and Gurib-Fakim, 2008
Lice repellent	Leafy branches used as lice repellent	Schmelzer and Gurib-Fakim, 2008
C. isomonensis Leandri		
Cough	Stem bark infusion taken orally	Schmelzer and Gurib-Fakim, 2008
Insect repellent	Leafy branches used as insect repellent	Schmelzer and Gurib-Fakim, 2008
C. *kimosorum* Leandri		
Antispasmodic	Leaf infusion taken orally	Rabehaja et al., 2014
Cough	Leaf infusion taken orally	Rabehaja et al., 2014
C. mongue Baill.		
Anorexia	Bark decoction used as tonic	Lemmens and Louppe, 2012
Blennorrhoea	Leaf and bark infusions applied topically or used in bathes	Lemmens and Louppe, 2012
Depression	Bark decoction used as tonic	Lemmens and Louppe, 2012
Fatigue	Bark decoction used as tonic	Lemmens and Louppe, 2012
C. myriaster Baker		
Epilepsy	Decoction of aerial shoots taken orally	Schmelzer and Gurib-Fakim, 2008
Headache	Decoction of aerial shoots inhaled	Schmelzer and Gurib-Fakim, 2008
Insect repellent	Leafy branches used as insect repellent	Schmelzer and Gurib-Fakim, 2008
C. nitidulus Baker		
Cough	Stem bark decoction taken orally	Schmelzer and Gurib-Fakim, 2008
Insect repellent	Leafy branches used as insect repellent	Schmelzer and Gurib-Fakim, 2008
Lice repellent	Leafy branches used as lice repellent	Schmelzer and Gurib-Fakim, 2008
Malaria	Stem bark decoction taken orally	Schmelzer and Gurib-Fakim, 2008
To clear nose	Leafy branches applied as steam bath	Schmelzer and Gurib-Fakim, 2008
C. sakamaliensis Leandri		
Cough	Bark infusion taken orally	Radulovic et al., 2006
Diarrhoea	Bark infusion taken orally	Radulovic et al., 2006
Fever	Bark infusion taken orally	Radulovic et al., 2006
Intestinal worms	Bark infusion taken orally	Radulovic et al., 2006

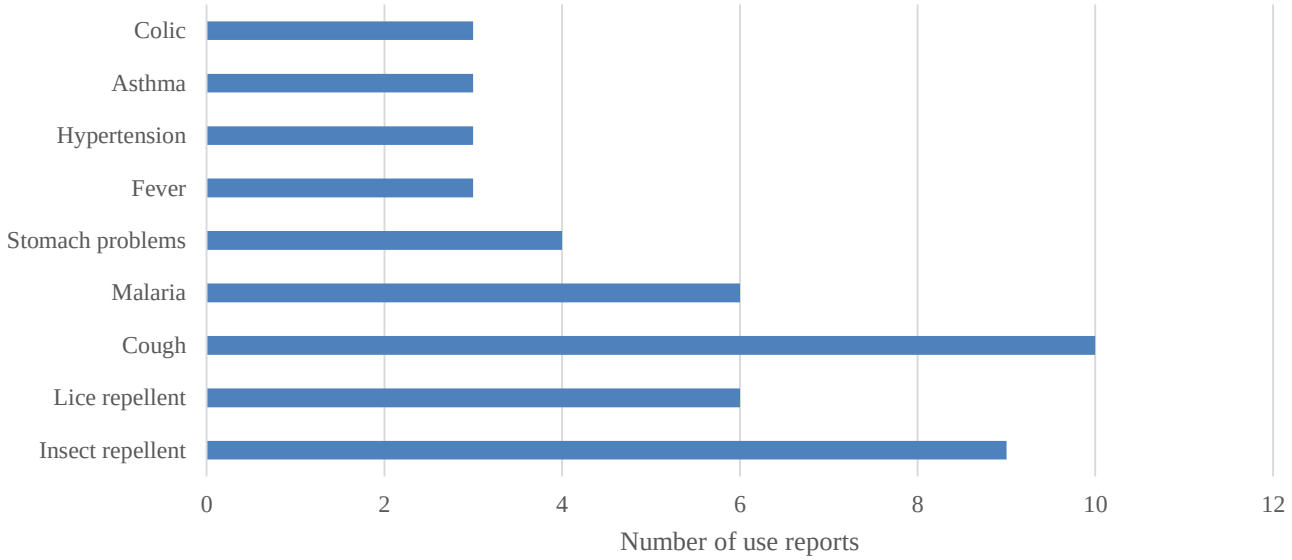

Figure 1: Main ethnomedicinal uses of *Croton* species in Madagascar

Many similarities can be recognized when the ethnomedicinal uses of *Croton* species are compared in terms of diseases or ailments treated and managed, plant parts used and herbal preparation and route of administration (Table 1). For example, leaf infusion of *C. ambanivoulensis* and *C. anisatus* is used as remedy for colic and dysentery (Schmelzer and Gurib-Fakim, 2008). The bark and leaf decoctions of *C. goudotii* and *C. mongue* are applied in bathes and lotions as remedies for blennorrhoea (Rakotonandrasana *et al*., 2010; Lemmens and Louppe, 2012). The leafy branches of *C. antanosiensis*, *C. barorum*, *C. bernierus*, *C. decaryi*, *C. greveanus*, *C. humbertii*, *C. isomonensis* and *C. nitidulus* are used as insect and lice repellents (Schmelzer and Gurib-Fakim, 2008). According to Schmelzer and Gurib-Fakim (2008) the leafy branches of *C. antanosiensis* and root and stem bark of *C. catatii* are used as disinfectant. Leaf, root and stem bark infusions and decoctions of *C. ambanivoulensis*, *C. anisatus*, *C. barorum*, *C. boinensis*, *C. geayi* and *C. sakamaliensis* are taken orally as remedies for diarrhoea, dysentery and stomach problems (Schmelzer and Gurib-Fakim, 2008; Radulovic et al., 2006; Rakotonandrasana *et al*., 2010). Decoction of leafy twigs, stem and root bark of *C. barorum*, *C. geayi* and *C. greveanus* are taken orally as remedies for asthma and hypertension (Palazzino et al., 1997; Schmelzer and Gurib-Fakim, 2008; Ruphin et al., 2016). The leaf, leafy twigs, stem and root bark infusions and decoctions of *C. barorum*, *C. bernierus*, *C. catatii*, *C. geayi*, *C. goudotii*, *C. greveanus*, *C. isomonensis*, C. *kimosorum*, *C. nitidulus* and *C. sakamaliensis* are taken orally as remedies for cough (Palazzino et al., 1997; Schmelzer and Gurib-Fakim, 2008; Rakotonandrasana et al., 2010; Ruphin et al., 2016). The leaf, root and stem bark decoctions of *C. barorum*, *C. catatii*, *C. geayi*, *C. goudotii*, *C. greveanus* and *C. nitidulus* are taken orally as remedies for malaria (Rasoanaivo et al., 1992; Palazzino et al., 1997; Schmelzer and Gurib-Fakim, 2008; Ruphin et al., 2016).

The stem bark (51.3%) and root bark (28.9%) are widely utilized, followed by aerial parts, leaves and leafy branches (Table 1). The use of stem bark and roots is unsustainable and will lead to reduced population size of the majority of *Croton* taxa in Madagascar. With increasing plant diversity loss through habitat transformation and over-exploitation of medicinal plant species throughout the world (William et al., 2013), there is need to assess the conservation status of endemic species to enable rapid and informed decisions to be made concerning conservation options. Williams et al. (2013) argued that plants used as herbal medicines are valuable for traditional practices of local communities.

Croton barorum and *C. geayi* are the most popular medicinal *Croton* species in Madagascar (Figure 2). The 38 human diseases and ailments treated by *Croton*

species in Madagascar are comparable to 24 diseases treated by *C. sylvaticus* Hochst. ex C. Krauss. (Maroyi 2017a). Research by Maroyi (2017c) revealed that *C. macrostachyus* Hochst. ex Delile is utilized as remedy 81 human and animal diseases including abdominal pains, cancer, gastro-intestinal disorders, malaria, pneumonia, sexually transmitted infections, skin infections, typhoid and wounds. Another *Croton* species widely utilized as traditional medicine in tropical Africa is *C. megalocarpus* Hutch., which is used as herbal medicine against 41 medical problems (Maroyi, 2012a, 2017b). *Croton megalocarpus* is used against gastro-intestinal problems, wounds, colds, fever and malaria, respiratory diseases, intestinal worms and cough (Maroyi, 2012a, 2017b). Results of this study and previous accounts from elsewhere show that *Croton* species have been an integral part of primary healthcare system in Madagascar, the tropics and subtropics since time immemorial.

Phytochemistry and biological activities

Ralison et al. (1986) isolated a toxic protein, monguine from seed extracts of *C. mongue* that inhibits protein synthesis. Krebs and Ramiarantosa (1996) isolated two clerodane-type furano-diterpenes, namely 3α,4β-dihydroxy-15,16-epoxy-12-oxo-cleroda-13(16),14-dien-9-al and 3α,4β-dihydroxy-15,16-epoxy-12-oxo-cleroda-13(16),14-diene, three triterpenes, 3β-acetoxy-friedoolean-14-en-28-oic acid, β-amyrin and friedelin and an alkaloid, 4-hydroxyhygrinic acid from methanolic bark extracts of *C. hovarum* (Table 2). In another study, Krebs and Ramiarantosa (1997) isolated clerodane and a nor-clerodane-type furano-diterpene 3,12-dioxo-15,16-epoxy-cleroda-13(16),14-dien-9-al and 3α,4β-dihydroxy-l5,l 6-epoxy-l 9-nor-12-oxo-cleroda-5(10),13(16),14-triene, and a flavonoid, vitexin from methanolic leaf extracts of *C. hovarum* (Table 2). Palazzino et al. (1997) isolated four diterpenes, namely geayine, 7-deoxogeayine, geayinine and isogeayinine from wood of *C. geayi* (Table 2). Radulović et al. (2006) showed that *C. antanosiensis*, *C. decaryi*, *C. geayi* and *C. sakamaliensis* contain essential oils with mono- and sesquiterpenes as the major components of their oils (Table 2). Rakotonandrasana et al. (2010) isolated two 3,4-seco-atisane diterpenoids, crotobarin and crotogoudin from the aerial parts of *C. barorum* and *C. goudotii* (Table 2). Rabehaja et al. (2014) isolated essentials oils from aerial, leaf and stems of *C. kimosorum* (Table 2). Ruphin et al. (2016) isolated essential oils from leaves of *C. barorum*, *C. geayi* and *C. greveanus* (Table 2).

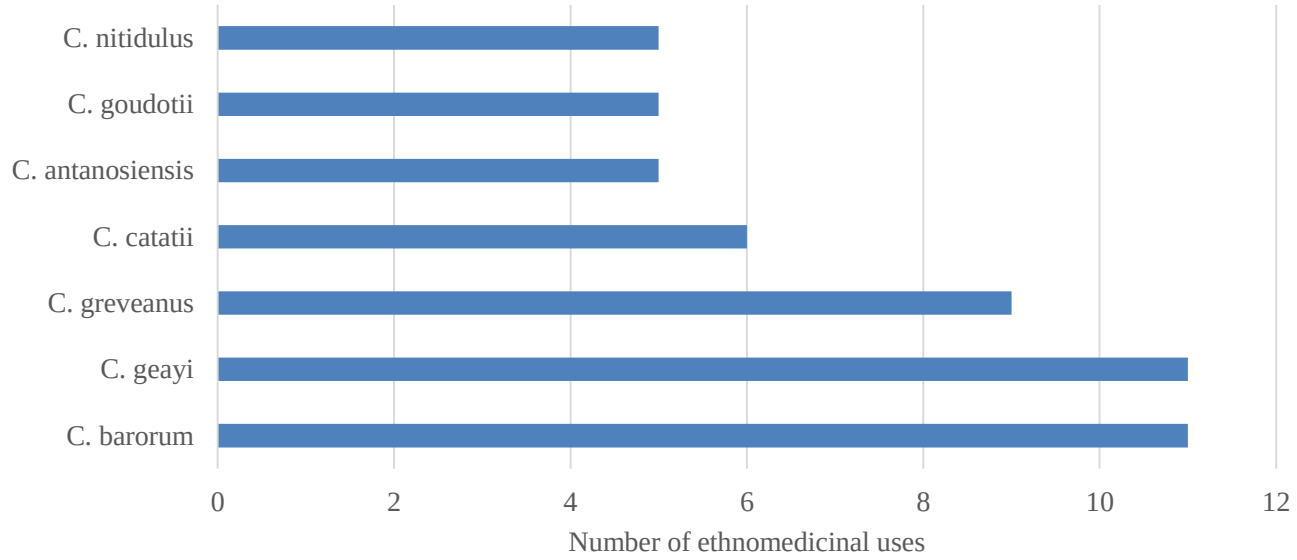

Figure 2: *Croton* species used as herbal medicines in Madagascar

Table 2: Phytochemical compounds reported from *Croton* species

Compound	Plant part	GC/MS phytochemical constituents	Method of compound analyses	References
C. antanosiensis				
Essential oil	Leaves, stems	Major compounds were onoterpenes, α-pinene, β-pinene, limonene and trans-nerolidol	GC/MS	Radulović et al., 2006
C. barorum				
3,4-seco-atisane diterpenoid	Aerial parts	Crotobarin	GC/MS	Rakotonandrasana et al., 2010
3,4-seco-atisane diterpenoid	Aerial parts	Crotogoudin	GC/MS	Rakotonandrasana et al., 2010
Essential oil	Leaves	Major compounds were β-phellandren, α-terpineol, camphene, α-pinene, germacrene and α-copaen	GC-FID and GC/MS	Ruphin et al., 2016
C. decaryi				
Essential oil	Leaves	Major compounds were β-caryophyllene, α-pinene, α-humulene, β-pinene and caryophyllene oxide	GC/MS	Radulović et al., 2006
Essential oil	Stems	Major compounds were α-pinene, borneol, camphene, β-caryophyllene, β-pinene and caryophyllene oxide	GC/MS	Radulović et al., 2006
C. geayi				
Essential oil	Leaves, stems	Major compounds were 1,8-cineole, β-caryophyllene, α-terpineol, γ-cadinene and τ-muurolol	GC/MS	Radulović et al., 2006
Essential oil	Leaves	Major compounds were β-pinene, limonene, trans hydrate sabinene, β-phellandrene, β-caryophyllene, α-pinene, trans-nerolidol and β-myrcen	GC-FID and GC/MS	Ruphin et al., 2016
Diterpene	Wood	Geayine	NMR	Palazzino et al., 1997
Diterpene	Wood	7-deoxogeayine	NMR	Palazzino et al., 1997
Diterpene	Wood	Geayinine	NMR	Palazzino et al., 1997
Diterpene	Wood	Isogeayinine	NMR	Palazzino et al., 1997
C. goudotii				
3,4-seco-atisane diterpenoid	Aerial parts	Crotobarin	GC/MS	Rakotonandrasana et al., 2010
3,4-seco-atisane diterpenoid	Aerial parts	Crotogoudin	GC/MS	Rakotonandrasana et al., 2010
C. greveanus				
Essential oil	Leaves	Major compounds were 1,8 cineol, linalol, trans hydrate sabinene, α-terpineol and sabinene	GC-FID and GC/MS	Ruphin et al., 2016
C. hovarum				
Furano-diterpene	Bark	3α,4β-dihydroxy-15,16-epoxy-12-oxo-cleroda-13(16),14-dien-9-al	NMR	Krebs and Ramiarantosa, 1996
Furano-diterpene	Bark	3α,4β-dihydroxy-15,16-epoxy-12-oxo-cleroda-13(16),14-diene	NMR	Krebs and Ramiarantosa, 1996
Alkaloid	Bark	4-hydroxyhygrinic acid	NMR	Krebs and Ramiarantosa, 1996
Triterpene	Bark	β-amyrin	NMR	Krebs and Ramiarantosa, 1996
Triterpene	Bark	3β-acetoxy-friedoolean-14-en-28-oic acid	NMR	Krebs and Ramiarantosa, 1996
Triterpene	Bark	Friedelin	NMR	Krebs and Ramiarantosa, 1996

Diterpene	Leaves	3,12-dioxo-15,16-epoxy-cleroda-13(16),14-dien-9-al	NMR	Krebs and Ramiarantosa, 1997
Diterpene	Leaves	3α,4β-dihydroxy-l5,l6-epoxy-l 9-nor-12-oxo-cleroda-5(10),13(16),14-triene	NMR	Krebs and Ramiarantosa, 1997
Flavonoid	Leaves	Vitexin	NMR	Krebs and Ramiarantosa, 1997
C. *kimosorum*				
Essential oil	Aerial parts	Major components were linalool, sabinene, 1,8-cineole, β-pinene, β-caryophyllene, terpinen-4-ol and geraniol	CC, GC, MS, NMR	Rabehaja et al., 2014
Essential oil	Leaves	Major components were sabinene, 1,8-cineole, β-pinene, β-caryophyllene and linalool	CC, GC, MS, NMR	Rabehaja et al., 2014
Essential oil	Stems	Major components were linalool, terpinen-4-ol, p-cymene, epi-α-bisabolol, τ-cadinol, 1,8-cineole and β-pinene	CC, GC, MS, NMR	Rabehaja et al., 2014
C. mongue				
Protein	Seeds	Monguine	TLC	Ralison et al., 1986
C. sakamaliensis				
Essential oil	Leaves	Major compounds were β-caryophyllene, caryophyllene oxide, 1.8-cineol, α-pinene and β-pinene	GC/MS	Radulović et al., 2006
Essential oil	Stem	Major compounds were 1.8-cineol, β-phellandrene, α-pinene, limonene and linalool	GC/MS	Radulović et al., 2006

Ruphin et al. (2016) evaluated antibacterial activities of leaf essential oils isolated from *C. barorum*, *C. geayi* and *C. greveanus* against *Bacillus subtilis*, *Bacillus cereus*, *Enterobacter cloacae*, *Escherichia coli*, *Salmonella typhii*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* using disc diffusion method with chloraphenicol or cycloheximid as controls. All bacteria demonstrated some degree of sensitivity to the essential oils isolated from *C. barorum* within the concentrations tested showing zone of inhibition ranging from 10.5 mm to 22.5 mm with the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values ranging from 1.25 µg/mL to 10.0 µg/mL (Ruphin et al., 2016). The leaf essential of *C. geayi* was inactive on *Enterobacter cloacae*, *Pseudomonas aeruginosa* and *Salmonella typhii*, but active against the rest of bacteria with zone of inhibition ranging from 3.2 mm to 10 mm, MIC and MBC values of 2.5 µg/mL to 5.0 µg/ mL (Ruphin et al., 2016). All bacteria demonstrated some degree of sensitivity to the essential oils isolated from *C. greveanus* within the concentrations tested showing inhibition zones ranging from 7.2 mm to 15 mm, MIC and MBC values of 0.312 µg/mL to 2.5 µg/mL (Ruphin et al., 2016). These findings corroborate the traditional uses and antibacterial potential of *C. barorum*, *C. geayi* and *C. greveanus* as traditional medicines for diarrhoea, gonorrhoea and stomach problems in Madagascar (Schmelzer and Gurib-Fakim, 2008; Ruphin et al., 2016).

Some *Croton* species are known to be poisonous and used as fishing and hunting poisons in the tropics and subtropics (Maroyi, 2012a,b; Maroyi, 2017a-c). A toxic protein, monguine was isolated from seed extracts of *C. mongue* by Ralison et al. (1986). The compound demonstrated median lethal dose (LD_{50}) value of 12 mg/kg of rat body weight after 24 hours. In Madagascar, the bark of *C. antanosiensis* is utilized as ordeal poison (Schmelzer and Gurib-Fakim, 2008), bark of *C. hovarum* is utilized as fish poison (Krebs and Ramiarontosa, 1996) and *C. barorum* is regarded as toxic (Rasoanaivo et al., 1992). Elsewhere in the tropics, the seed oil of *C. macrostachyus* is used as fish poison in Ethiopia, stem bark of *C. tchibangensis* Pellegrin is used as fish poison in Gabon and ripe seeds of *C. tiglium* L. are widely used as fishing and hunting poison in tropical Asia (Neuwinger, 2000). The diterpenoids of *Croton* species are also known to be toxins that are irritant to mucosas and the body skin (Bruneton, 1995) and also these compounds are responsible for a burning sensation caused in the mouth and throat (Watt and Breyer-Brandwijk, 1962). Rakotonandrasana et al. (2010) evaluated cytotoxic activities of ethyl acetate shoot extract of *C. goudotii* and *C. barorum* and compounds crotobarin and crotogoudin isolated from the two taxa using murine lymphocytic leukemia P388 cell line with

camptothecin as a positive control. The extracts exhibited very strong cytotoxic activities with 100 % inhibition at 10 μg/mL against the P388. The compounds crotobarin and crotogoudin isolated from *C. goudotii* and *C. barorum* exhibited strong cytotoxic activities with IC_{50} value of 0.13 ± 0.01 μg/mL and 0.14 ± 0.05 μg/mL, respectively, against the murine P388. The potent cytotoxic activities demonstrated by extracts and compounds isolated from *C. barorum* and *C. goudotii* implies that these species have potential as herbal medicines against cancer-related diseases. Therefore, these results support the use of stem and root bark decoction of *C. barorum* against breast cancer and leukemia in Madagascar (Schmelzer and Gurib-Fakim, 2008; Rakotonandrasana et al., 2010).

Conclusion

Many phytochemical constituents and ethnomedicinal applications of *Croton* species that are endemic to Madagascar have been demonstrated in this study. Whilst some research has been done on ethnomedicinal uses and phytochemical constituents, there is not sufficient data to correlate most ethnomedicinal applications with the documented biological activities. If sustainable utilization and maximum pharmaceutical benefits are to be derived from *Croton* species in Madagascar, there is need for necessary information about ethnobotanical uses, phytochemistry, pharmacological properties, conservation status and therapeutic potential of the species. Most of the pharmacological research conducted on *Croton* species in Madagascar have focused on assessing the fixed and volatile constituents of the species, and little research has been done on the pharmacological properties of the chemical compounds and crude extracts of the species. Detailed phytochemical studies and phytochemical properties, especially the mechanisms of action of the bioactive constituents is necessary to illustrate the correlation between medicinal uses and biological activities of the extracts. However, because *Croton* taxa contain potentially toxic compounds, their toxicological properties need to be properly established.

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