

Original Research Article

Ethnomedicinal uses and pharmacological activities of *Croton megalobotrys* Müll Arg: A systematic review

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Sent for review: 9 March 2017

Revised accepted: 8 September 2017

Abstract

Purpose: To provide an overview of the ethnomedicinal uses and pharmacological activities of *Croton megalobotrys* as to understand its potential value and importance in primary health care systems of local communities throughout its distributional range.

Methods: The literature search for information on ethnomedicinal uses and pharmacological activities of *C. megalobotrys* was undertaken using databases such as Web of Science, BMC, Science Direct, Elsevier, Scopus, PubMed and Scielo. Other relevant literature sources included books, book chapters, websites, theses, conference papers and other scientific publications.

Results: *Croton megalobotrys* is an important herbal medicine in southern Africa used as an abortifacient and purgative, and as remedy for human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) opportunistic infections, malaria, muscle aches or pain, sexually transmitted infections (STIs) and skin infections. The chemical constituent of *C. megalobotrys* is mainly composed of alkaloids and cinnamate derivative isolated from the stem bark. The biological activities demonstrated include antibacterial, antiplasmodial, anti-HIV and radical scavenging activities.

Conclusion: The historical traditional usage of *C. megalobotrys* as herbal medicine in southern Africa calls for detailed phytochemical and pharmacological properties of the species aimed at identifying the compounds responsible for its wide usage as an herbal medicine.

Keywords: Alkaloids, *Croton megalobotrys*, Ethnopharmacology, Primary health, Southern Africa

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Boline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Medicinal plants play an important role in managing and treating human and animal diseases and ailments throughout the world. According to van Wyk *et al* [1], plants are an important primary source of most medicines in the world and they still continue to provide humans with new herbal medicines. It is within this context that the ethnomedicinal uses pharmacological activities of *Croton megalobotrys* Müll. Arg. were evaluated. *Croton megalobotrys* is a member of the *Croton* genus

of the Euphorbiaceae family, comprising about 1300 species worldwide [2]. According to Salatino *et al* [2], several *Croton* species are widely used as traditional medicines in Africa, Asia and South America. Research by several authors [3-8] revealed that *C. megalobotrys* is an important medicinal plant used by both rural and urban communities throughout its native distributional range in tropical Africa. *Croton megalobotrys* is traded as medicinal plant in herbal medicine (*muti*) markets or shops in the Mpumalanga province in South Africa [9]. Research done by Tshisikhawe *et al* [10] showed that harvesting of stem bark of *C. megalobotrys*

for medicinal purposes may threaten the survival of the species in the Limpopo province in South Africa where the species is harvested from the wild as herbal medicine. Therefore, this review is aimed at assessing if there is correlation between the ethnomedicinal uses of *C. megalobotrys* and the documented phytochemical and pharmacological properties of the species. It is hoped that this ethnomedicinal and pharmacological information will highlight the value and importance of *C. megalobotrys* as a potential source of a wide range of pharmaceutical products in southern Africa and will provide useful information to other researchers interested in the plant species.

METHODS

The literature search for information on ethnopharmacology and therapeutic value of *C. megalobotrys* (i.e., its ethnomedicinal uses, including other traditional uses, its botany, distribution, phytochemistry and pharmacological properties of the species) was performed from September 2016 to March 2017. Publications from all years included in databases such as BMC, Elsevier, PubMed, Scielo, Science Direct, Scopus and Web of Science were considered. Other literature sources were obtained from the library collections at the University of Fort Hare, Alice campus, South Africa, including scientific papers published in books, book chapters, international journals, theses, conference papers and other scientific publications. The keywords used in the search included "*Croton megalobotrys*", the synonym of the species "*Croton gubouga* S. Moore", and English names such as "fever bark", "fever bark tree", "fever-berry", "fever-berry croton", "large fever-berry" and "lowveld croton". All articles that appeared to meet the selection criteria were retrieved, and this review draws heavily on the research results published in international journals (33), books (13), websites (four), book chapters, dissertations and theses (three each), conference reports and scientific reports from international organizations (one each). Most of the ethnomedicinal uses data on *C. megalobotrys* have been collected from Zimbabwe, Zambia, South Africa, Namibia, Mozambique, Malawi and Botswana.

RESULTS

Botanical profile of *Croton megalobotrys*

The generic name "*Croton*" was derived from a Greek word "kroton" meaning thick, in reference to the thick and smooth seeds [11], a common feature of most *Croton* species which belong to the Crotonoideae subfamily of the

Euphorbiaceae family [12-14]. The specific name "*megalobotrys*" was derived from Greek words meaning "big bunch of grapes" in reference to the big bunches of fruits, characteristic of the species [11,12,15,16]. The synonym of *C. megalobotrys* is *C. gubouga* S. Moore [12-16]. *Croton megalobotrys* has been recorded in Botswana, Zimbabwe, Zambia, Malawi, South Africa, Mozambique and Namibia (Figure 1). *Croton megalobotrys* is common in semi-deciduous savannah, at medium to low altitudes on alluvial soils and usually a constituent of riverine and swamp fringe forest or thicket [12-17].

Croton megalobotrys is a shrubby to medium-sized, densely leafy tree reaching 15 m tall [17] with a stem up to 60 cm in diameter [13]. The bark is pale grey, smooth at first with vertical lines of lenticels, becoming rough and fissured in older trees. The leaves are ovate, roughly triangular with silvery green hairs on the under surface, 3-19 cm long and 1-13 cm wide [13]. The flowers are pale cream to yellowish green in colour, with either only male or female flowers or mixed and then with male flowers in upper part and one to several female flowers at the base [17]. The fruit is a rounded to ellipsoid drupe covered with whitish short hairs.

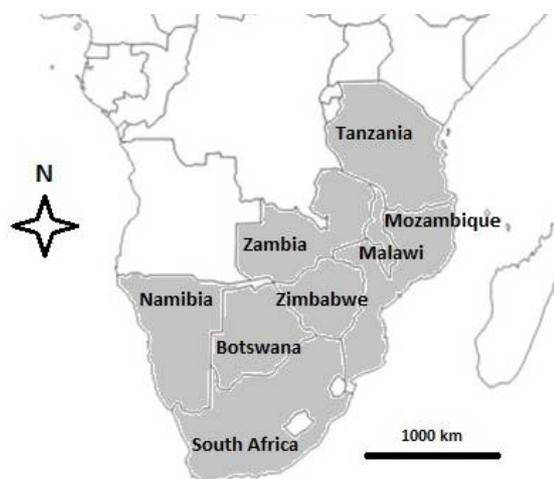


Figure 1: Distribution of *Croton megalobotrys* in southern Africa

Vernacular names and traditional uses of *Croton megalobotrys* in southern Africa

There appear to be a direct correlation between the number of vernacular names and the traditional uses of *C. megalobotrys* in southern Africa (Figure 2). Literature search revealed that *C. megalobotrys* has no fewer than 62 vernacular names in southern Africa (Table 1), with South Africa having 21 vernacular names followed by Botswana with 20, Zimbabwe with eight and

Namibia with six vernacular names (Table 1). Botswana has the highest number of uses of *C. megalobotrys*, 20 in total (Table 2) followed by South Africa with nine, Zimbabwe with seven and Malawi with six uses (Table 2). These findings support an observation made by Maroyi [18] that plant species characterized by several vernacular names implies that such species are useful to local people as they rarely give vernacular names to plants that are not useful to them. This study revealed that *C. megalobotrys* has vernacular names and traditional uses in 87.5% of the countries where it is indigenous (Tables 1 and 2), with the exception of Tanzania where no vernacular names or traditional uses have been recorded. *Croton megalobotrys* is commonly referred to as “fever-berry” in 62.5% of the countries where it is indigenous, these include Zimbabwe, Botswana, Namibia, Malawi and South Africa (Table 1). *Croton megalobotrys* got such a common name mainly because the seeds and bark of the species have considerable reputation among local communities as remedy for fever or malaria [12-14,17,19]. Literature records indicate that on 30 September 1899, a medical officer, Dr John Maberly used bark and seeds of *C. megalobotrys* mixed with opium (*Papaver somniferum* L.) as remedy for malaria [20]. According to Coates Palgrave [17], *C. megalobotrys* bark and seeds are well known among local communities in southern Africa and early pioneers in malarial areas not only as a cure for fever but also as a prophylactic. Other common names which allude to the usage of *C. megalobotrys* as herbal medicine for fever or

malaria include “fever bark”, “fever bark tree”, “fever-berry cotton”, “large fever-berry” and “river fever-berry” (Table 1). The Afrikaans vernacular name “grootkoorsbessie” is a contraction of three words “groot”, “koors” and “bessie” which translate to “large”, “fever” and “berry” respectively in English, suggesting that the large fruits (berries) characteristic of the species are used against fever.

The bark, fruits, leaves, roots and seeds of *C. megalobotrys* are used as herbal medicines for 35 and two human and animal diseases respectively (Table 2). The bark or root infusion of *C. megalobotrys* is taken orally as an abortifacient and purgative or as herbal medicine for ascites also known as dropsy or pain in the alimentary canal in Malawi and Zimbabwe [4,5,39]. In Malawi, bark decoction of *C. megalobotrys* is applied on fresh wounds or cuts while leaf or root decoction is taken orally as remedy for headaches [7]. In Zimbabwe, root bark powder of *C. megalobotrys* is taken orally as remedy for female infertility [5] and bark or root decoction is taken orally as remedy for malaria [4]. Bark decoction of *C. megalobotrys* is also taken orally as herbal medicine for malaria in Mozambique [3] and Namibia [41]. In Botswana and South Africa, seeds or bark and root decoction of *C. megalobotrys* are taken orally as purgative [3,6,17,24,28,32] or as herbal medicine for fever or malaria [3,12,17,21,24,34] or berries are applied as poultices for skin infections or muscle aches or pain [24,35].

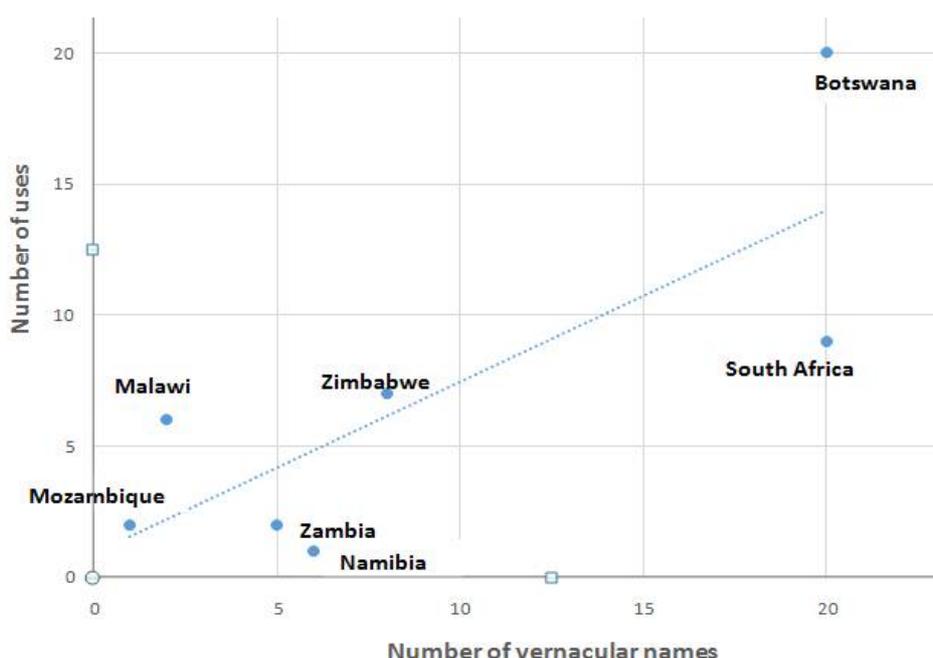


Figure 2: Relationship between the number of vernacular names and traditional uses of *Croton megalobotrys* in southern Africa

Table 1: Vernacular names of *Croton megalobotrys* in southern Africa

Vernacular names and ethnic group in brackets	Country	References
Fever-berry, large fever-berry, river fever-berry (English), mobwiti, moêpê, mokungulu, moshoholo, moshoole, motlogatloga, motsêbê, motukatuka, mukungulu, mutsebi, phofutsa, phokotsa, phufutsa, phukutsa, pokudza, pukhutsa (Setswana), okayi (Seyei)	Botswana	[8,11,21-29]
Mtutumuko (Chewa), fever-berry (English)	Malawi	[7,15]
Chungué-chungué (Chindau)	Mozambique	[30]
Grootkoorsbessie (Afrikaans), fever-berry, large fever-berry (English), mununkila, murongo, mutwatwa (Silozi)	Namibia	[31]
Grootkoorsbessie, koorsboom (Afrikaans), fever-bark, fever bark tree, fever-berry, large fever-berry, lowveld croton (English), mohlukohloko (Pedi), moêpê, mosôôlê, motsêbê, motshebe, motsibi, mutsebi, phukutsa (Setswana), lijaha (Sotho), nxunguxungu, nxungwexungwe, shungweshungwe, xunguxungu (Tsonga), muruthu (Venda)	South Africa	[3,6,9,12,17,32-35]
Muchape (Kore-kore), mtutu (Kunda), munanga (Kunda, Nsenga), mutua, mutuatua (Tonga/Tokaleya/Lozi)	Zambia	[36-38]
Fever-berry, fever-berry croton (English), umtshape (Ndebele) mubvukuta, muchape, mugubvuka, mushape (Shona), mutonga (Tonga)	Zimbabwe	[4,16,17,39,40]

The bark, leaf, root or seed decoction of *C. megalobotrys* is taken orally as herbal medicine for sexually transmitted infections (STIs) in Zambia [37] and other STIs such as gonorrhoea in Zambia [38] and venereal diseases in South Africa [6]. Research done by Mabogo [6] revealed that seed decoction of *C. megalobotrys* is taken orally as herbal medicine for kidney problems and purification of the blood. In Botswana, root infusion of *C. megalobotrys* is taken orally for fattening babies [11] and seed decoction of the species is taken orally as laxative [22]. Recently, research done by Tietjen *et al* [8] in Botswana revealed that *C. megalobotrys* is widely used to treat or manage human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) opportunistic infections such as diarrhoea, loss of appetite and stomach problems.

Croton megalobotrys is used as ethnoveterinary medicine by the resource-limited farmers in Botswana as an alternative to orthodox pharmaceuticals. Leaf decoction of *C. megalobotrys* is applied on lumpy skin [27] and bark or leaf decoction is also applied on animal sores or wounds [29]. *Croton megalobotrys* stem bark is widely used as a fish poison in Botswana [21,23], Mozambique [3] and South Africa [3,42]. *Croton megalobotrys* also provides varied products throughout its distributional range and these include construction poles, timber and firewood. According to Mutakela [43], *C. megalobotrys* is an important source of timber and other non-woody plant products in rural areas of Botswana. In Botswana, *C. megalobotrys* is browsed by game and livestock [44] and its leaf decoction is used as a pesticide, usually sprayed on arable land to kill worms [29]. Research by Hamilton *et al.* [45], and Raman and Kandula [46] showed that *C. megalobotrys* is

used as a stimulant by chacma baboons (*Papio ursinus*). Chacma baboons in South Africa are known to consume each day a little quantity of leaves of the species, which is not classified as the baboon's regular diet [45,46]. Consumption of *C. megalobotrys* is not directly related to any illness but for its stimulant activity [46]. *Croton megalobotrys* is planted as an ornamental and shade plant in rural areas of Botswana [29].

DISCUSSION

Correlation between ethnomedicinal uses and pharmacological activities of *C. megalobotrys*

Aligning the available ethnomedicinal information about *C. megalobotrys* in southern Africa, it appears that the species is most commonly used as an abortifacient, fish poison, purgative and as herbal medicine for the treatment and management of HIV/AIDS opportunistic infections, malaria and STIs (Figure 3). Several other *Croton* species including *C. macrostachyus* Hochst. ex Delile, *C. megalocarpus* Hutch. and *C. sylvaticus* Hochst. ex C. Krauss. are widely used as purgatives [48-50]. The seeds of *C. tiglium* L. are the sources of a commercially produced and marketed croton oil widely used as a purgative [2]. *Croton megalobotrys* also plays an important role in the treatment and management of HIV/AIDS and malaria which were classified among the top five killer diseases in Africa in 2012 by the World Health Organization. Research by Ramjee *et al.* [51] revealed that STIs are among the most prevalent infectious diseases worldwide and approximately 1 million women in Africa die yearly due to infection with HIV/AIDS and STIs. Whilst *C. megalobotrys* has proved to be useful over the centuries as herbal medicine for some of these important diseases in Africa, no meaningful

phytochemical and pharmacological analyses exist in literature linking active principles of the species to its ethnomedicinal uses.

Apart from 4-hydroxyhygric acid isolated from the bark of *C. megalobotrys* by Goodson and Clewer [19] and a cinnamate derivative (*E*)-tetratriacontyl-3-(4-hydroxy-3-methoxyphenyl)-2-propenate (Figure 4) isolated from the chloroform fraction of the stem bark extract by Abosi and Majinda [52], little is known about the chemical constituents of the species. But genus *Croton* is known to have a wide range of chemical compounds including alkaloids, cardenolides, diterpenoids, flavonoids, saponins, mono and

sesquiterpenoids [2,53]. The diterpenoids isolated from other species of the *Croton* genus are regarded as toxic irritants of the skin and mucosae [54] and they produce a burning sensation in the throat and mouth [3,19].

Selowa *et al* [35] evaluated antibacterial activities of *n*-hexane, dichloromethane, ethyl acetate, acetone and methanol leaf powder extract of *C. megalobotrys* against Gram negative bacteria *Enterococcus faecalis* and *Escherichia coli*, and Gram positive bacteria *Pseudomonas aeruginosa* and *Staphylococcus aureus* using bioautograph and micro-dilution techniques.

Table 2: Traditional uses of *Croton megalobotrys* in southern Africa

Use	Plant parts used	Country practiced	References
Abortifacient	Bark or root decoction taken orally	Zimbabwe	[4,5,39]
Ascites (dropsy)	Bark or root infusion taken orally	Malawi, Zimbabwe	[4,5]
Cuts	Bark decoction applied on affected body part	Malawi	[7]
Diarrhoea of HIV patients	Bark decoction taken orally	Botswana	[8]
Fattening of babies	Root infusion taken orally	Botswana	[11]
Female infertility	Root bark powder taken orally	Zimbabwe	[5]
Fever	Seed taken orally	Botswana, South Africa	[24,34]
Gonorrhoea	Leaf decoction taken orally	Zambia	[38]
Headache	Leaf or root decoction taken orally	Malawi	[7]
HIV/AIDS	Bark decoction taken orally	Botswana	[8]
Kidneys problems	Seed decoction taken orally	South Africa	[6]
Laxative	Seed decoction taken orally	Botswana	[22]
Loss of appetite	Bark decoction taken orally	Botswana	[8]
Malaria	Bark, root, seed decoction	Botswana; Mozambique, Namibia, South Africa, Zimbabwe	[3,4,21,24,41]
Malaria	Bark and seed mixed with opium (<i>Papaver somniferum</i> L.)	South Africa	[20]
Muscle aches or pain	Berries applied on affected body part as poultices	Botswana, South Africa	[24,35]
Pain in alimentary canal	Bark powder taken orally	Malawi, Zimbabwe	[5]
Purgative	Bark, root or seed decoction taken orally	Botswana, Malawi, South Africa, Zimbabwe	[3-6,24,28,32]
Purification of blood	Seed decoction taken orally	South Africa	[6]
Sexually transmitted infections (STIs)	Bark or root decoction taken orally	Zambia	[37,47]
Skin infections	Berries applied as poultices on affected body part	Botswana, South Africa	[24,35]
Stomach problems	Bark decoction taken orally	Botswana	[21]
Venereal diseases	Seed decoction taken orally	South Africa	[6]
Ethno-veterinary medicine			
Lumpy skin	Leaf decoction applied on sores	Botswana	[27]
Wounds	Bark and leaf decoction applied on wounds	Botswana	[29]
Other uses			
Browse for game and livestock		Botswana	[44]
Construction timber		Botswana	[11,29]
Fuel wood		Botswana	[26]
Fish poison	Bark, leaves and fruits used	Botswana, Mozambique, South Africa	[3,21,23,42]
Kill worms in arable land	Leaf decoction sprayed on arable land	Botswana	[29]
Ornamental		Botswana	[22]
Shade		Botswana	[29]

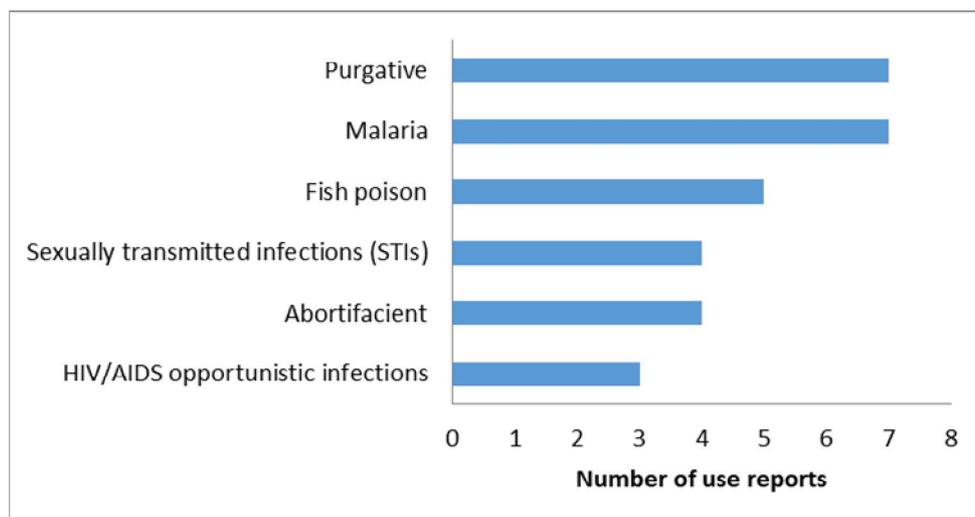


Figure 3: Main traditional applications of *Croton megalobotrys* in southern Africa. A traditional use is only counted once per publication

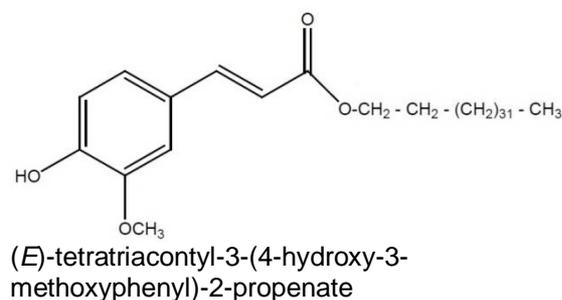
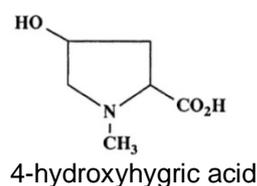


Figure 4: Chemical structures of compounds isolated from the bark of *Croton megalobotrys*

All extracts showed antibacterial activities, with the highest activity observed against *Enterococcus faecalis* with a minimal inhibitory concentration (MIC) value of 0.02 mg/ml [35]. These findings somehow support the species' antibacterial potential and its usefulness in its traditional usage as herbal medicine for diarrhoea [8], gonorrhoea [38], skin infections [24,35], STIs [37], stomach problems [8] and venereal diseases [6]. More research is recommended focusing on antibacterial activities of *C. megalobotrys* against known bacterial pathogens such as *Neisseria gonorrhoeae* which cause gonorrhoea, and other bacterial pathogens such as *Shigella dysenteriae*, *Shigella flexneri* and *Vibrio cholerae* which cause gastrointestinal infections.

Abosi and Majinda [52] evaluated antiplasmodial activities of root, stem bark and leaf extracts of

C. megalobotrys in NMRI white albino mice infected with 1×10^7 *Plasmodium berghei* (ANKA) parasitized erythrocytes. The effects of the extracts were assessed on early infection, established infection and the residual effect of the extracts was also assessed using the Repository or Prophylactic test. The stem bark extract produced a suppressive effect of 74.5 % in early infection and a residual inhibitory effect of 86.9 %. In an established infection, a mean survival time of 16.2 days was achieved although parasitaemia was not completely eliminated. Antiplasmodial activity was observed in *in vitro* test with IC_{50} values of $1.74 \pm .47 \mu\text{g/ml}$ and $3.78 \pm 1.03 \mu\text{g/ml}$ for the hexane fraction of the stem bark extract against chloroquine sensitive (D6) and chloroquine-resistant (W2) strains of *Plasmodium falciparum* respectively [52]. The antiplasmodial activity demonstrated in this study support the folkloric use of *C. megalobotrys* for treating and managing malaria in southern Africa and also using the species as prophylactic medicine for malaria [3,4,20,21,24]. Previous research by Ndunda [53] revealed that over 70 % of species belonging to the *Croton* genus reported in ethnomedicinal treatment of malaria and tested for antiplasmodial activities were found to be active, an indication of the potential of these species as antimalarial remedies. The preliminary radical scavenging evaluation carried out by Abosi and Majinda [52] using the chloroform fraction in qualitative 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay showed activity at a loading dose of 0.05 μg , thus exhibiting radical scavenging activity comparable to that of ascorbic acid. Collectively, data obtained by Abosi and Majinda [52] indicate that *C. megalobotrys* suppresses free radical formation, however, determining the exact mechanisms of action will require further investigations.

Tietjen *et al* [8] evaluated the crude extracts of *C. megalobotrys* for *in vitro* cytotoxicity and inhibition of wild-type (NL4.3) and ARV-resistant HIV-1 replication in an immortalized GFP-reporter CD4₊ T-cell line. The study by Tietjen *et al* [8] is based on the wide use of *C. megalobotrys* as herbal medicine for treating and managing HIV/AIDS in Botswana where in some cases the species is used concurrently with standard ARVs. *Croton megalobotrys* bark extracts inhibited HIV-1NL4.3 replication with dose-dependence and without concomitant cytotoxicity and inhibited HIV-1 replication by a maximum of 45 % at concentrations as low as 0.05 mg/ml. According to Tietjen *et al* [8], *C. megalobotrys* extracts did not interfere with antiviral activities of licensed ARVs when applied in combination and exhibited comparable efficacies against viruses harboring major resistance mutations to licensed protease, reverse-transcriptase, or integrase inhibitors. Based on these findings, *C. megalobotrys* can therefore, be administered in parallel with Western HIV/AIDS treatments in managing the effects of HIV/AIDS in Botswana, a disease that has become a devastating epidemic in sub-Saharan Africa [55].

Toxicity evaluation

A number of ethnobotanical studies have highlighted the toxicity of *C. megalobotrys* when used as herbal medicine. *Croton megalobotrys* is a well-known poisonous plant in South Africa [32,56] and Zimbabwe [4,5,40,57], although it is widely used as herbal medicine in both countries. According to Gelfand *et al* [5], taking of bark and root of *C. megalobotrys* has been reported to cause swelling of testicles in Zimbabwe. Mabogo [6] emphasized the need to follow traditional healers' dosage instructions when using *C. megalobotrys* as a purgative, since there is a possibility of fatal side effects. It is commonly recommended that an adult should take one or three quarters of a seed at a time [6]. Preliminary toxicity investigations showed that ground bark of *C. megalobotrys* caused purgation and emesis in dogs, but rabbits were less sensitive although in doses of 1 g/kg of body weight induced diarrhoea [19]. In human beings, administration of *C. megalobotrys* bark causes intense burning sensation in the throat, salivation and slight nausea with slight laxative effect [3,19]. The toxicity effects of *C. megalobotrys* are attributed to toxic diterpenes which are characteristic of most species belonging to the *Croton* genus [58]. No detailed cytotoxicity or toxicity effects of *C. megalobotrys* have been undertaken recently, although it is clear that detailed toxicity studies

for such a widely used medicinal plant in southern Africa are required.

CONCLUSION

The historical traditional usage of *C. megalobotrys* as herbal medicine in southern Africa calls for detailed phytochemical and pharmacological properties of the species aimed at identifying the compounds responsible for its wide usage as herbal medicine. At the present moment, there is not yet enough systematic data regarding phytochemistry, pharmacological properties and clinical research of *C. megalobotrys* extracts and compounds. There are very few to nil experimental studies, clinical research trials and target-organ toxicity studies involving *C. megalobotrys* extracts and its compounds that have been carried out so far. Given this background, it is quite difficult to correlate the ethnomedicinal uses of the species with the few phytochemical profiling and pharmacological evaluations that have been done so far. There is need therefore, to evaluate pharmacological properties of the species, as these may be directly related to the species ethnomedicinal uses. Detailed pharmacological studies will provide some insight into the therapeutic potential of *C. megalobotrys*. Since *C. megalobotrys* is classified as poisonous in southern Africa [4-6,32,40,56], there is need for a detailed toxicological assessment of the species using reliable analytical methods.

DECLARATIONS

Acknowledgement

Financial support of this work by the National Research Foundation (NRF) and Govan Mbeki Research and Development Centre (GMRDC), University of Fort Hare is gratefully acknowledged.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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