ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 11, Issue 10, 2018

Online - 2455-3891
Print - 0974-2441

Review Article

A REVIEW OF THE ETHNOMEDICINAL USES, PHYTOCHEMISTRY AND PHARMACOLOGICAL PROPERTIES OF *EKEBERGIA CAPENSIS* SPARRM

ALFRED MAROYI*

Department of Botany, Medicinal Plants and Economic Development Research Centre, University of Fort Hare, Private Bag X1314, Alice 5700, South Africa. Email: amaroyi@ufh.ac.za

Received: 07 August 2018, Revised and Accepted: 29 August 2018

ABSTRACT

Ekebergia capensis is an integral part of indigenous pharmacopeia in tropical Africa. The present study critically reviewed the ethnomedicinal uses, phytochemistry, and pharmacological properties of *E. capensis*. The keywords including *E. capensis*, its synonyms, English common names, ethnomedicinal uses, and phytochemistry and pharmacological properties of the species were searched using electronic databases such as ISI web of knowledge, ProQuest, science direct, OATD, Scopus, Open-thesis, PubMed, and Google Scholar. Pre-electronic literature search of conference papers, scientific articles, books, book chapters, dissertations, and theses was carried out at the University Library. Literature studies revealed that *E. capensis* is mainly used as herbal medicine against fever and malaria, gastrointestinal problems, pain, parasitic worms, reproductive problems in women, respiratory problems, and skin diseases. Phytochemical compounds identified from the species include alkaloids, anthraquinones, coumarins, flavonoids, glycoflavonoids, glycosides, iridoids, limonoids, polyphenols, phytosteroids, pregnane, saponins, tannins, and withanolides. Pharmacological studies revealed that *E. capensis* extracts and compounds have acetylcholinesterase-inhibitory, analgesic and anti-inflammatory, anthelmintic, antibacterial, antifungal, antigonococcal, antimycobacterial, antimycoplasmal, antihypertensive, antioxidant, antimalarial and antiplasmodial, antischistosomal, antitrypanosomal, and antiviral and cytotoxicity activities. Although pharmacological evaluations carried out so far have confirmed the potency of *E. capensis* crude extracts and compounds, detailed studies are required aimed at establishing the efficacy, clinical relevance, safety, and mechanisms of action of the plant extracts and compounds.

Keywords: *Ekebergia capensis*, Meliaceae, Traditional medicine, Tropical Africa.

 DOI: http://dx.doi.org/10.22159/ajpcr.2018.v11i10.28816

INTRODUCTION

Ekebergia capensis Sparrm. (Family Meliaceae) is an important component of the indigenous pharmacopeia in South Africa where the bark, sometimes the leaves or roots are used as an emetic, vermifuge, abscesses, acne, acute gastritis, boils, chronic cough, dysentery, headache, heartburn, and scabies [1]. According to George *et al*. [2], *E. capensis* has potential as a commercial source of the compound limonoid ekebergin for vermifuge and emetic drugs. *E. capensis* is an integral part of the Materia Medica in South Africa, used regularly and included in the book "medicinal plants of South Africa" written by Van Wyk *et al*. [1]. Based on its wide application as herbal medicine, the bark of *E. capensis* is marketed as traditional medicine in informal herbal medicine markets and other informal markets in Gauteng and KwaZulu Natal provinces in South Africa [3,4]. According to Neuwinger [5], the leaves, roots, and stem bark of *E. capensis* are used as fish poison in the Democratic Republic of Congo (DRC) and Nigeria. The family Meliaceae is pantropical in distribution, consisting of trees and shrubs recorded in rainforests, with some taxa confined to seasonally dry forests, mangroves, and tropical woodlands [6]. At the present moment, about 50 genera and 700 species are recognized in the family worldwide [6,7]. Close to a third of these species (223 species) are threatened with extinction, listed in the 2018 IUCN Red List of Threatened Species as critically endangered, vulnerable, or endangered [8]. Among these are *Entandrophragma candollei* Harms, *Entandrophragma angolense* (Welw.) C. DC., *Entandrophragma utile* (Dawe and Sprague) Sprague, *Entandrophragma cylindricum* (Sprague) Sprague, *Khaya grandifoliola* C. DC., *Khaya anthotheca* (Welw.) C. DC., *K. madagascariensis* Jum. and Perr., *K. ivorensis* A. Chev., and *Khaya senegalensis* (Descr.) A. Juss. which are listed as vulnerable or endangered [8] and used as timber and traditional medicines in tropical Africa [9]. In recent years, members of the Meliaceae family have attracted considerable attention as an important source of limonoids and tetranortriterpenoids with insecticidal, antifeedant, and other pharmacological properties [10]. It is within this context that the chemical composition, pharmacological properties, and medicinal uses of *E. capensis* were reviewed aimed at evaluating the therapeutic potential of the species.

BOTANICAL PROFILE OF *E. CAPENSIS*

The genus *Ekebergia* sparrm. is in honor of a Swedish physician and chemist, Captain Carl Gustaf Ekeberg (1716–1784), whose sponsorship in the 18th century made it possible for Anders Sparrman, the author of the genus and the species *E. capensis* to visit Africa [11,12]. The specific name "capensis" means "from the Cape" in reference to the Cape province in South Africa where the type specimen was collected from. The genus *Ekebergia* consists of four species globally, *E. capensis, Ekebergia benguelensis* Welw. ex C. DC., *Ekebergia pterophylla* (C. DC.) Hofmeyr, and *Ekebergia pumila* I. M. Johnst [11,13,14]. *E. capensis* is a semi-deciduous or evergreen, large to medium-sized tree growing up to 100 cm in diameter and 35 m in height [11,12,15]. The bole is usually straight or sometimes crooked, branchless for up to 12 cm; stem may be swollen, buttressed and fluted in forests or short, and unfluted in open woodland [11]. The young stems are dotted circular leaf scars and whitish lenticels. Leaves are compound, alternate or crowded at the ends of branchlets. The leaflets are 3–7 pairs per leaf, glossy green in color, margin entire and may be waxy, with an asymmetric base, sessile, opposite, with a terminal leaflet and sometimes with a drip-tip [15]. Flowers are small, greenish-yellow, or white in color, sweetly scented, with male and female flowers on different trees. Fruits are fleshy and succulent, subglobose, pink to bright red in color when ripe [11]. The seeds are white in color and oval in shape; a fruit usually produces 2–4 seeds [11,15].

E. capensis is widespread in tropical and subtropical Africa, from Senegal east to Eritrea and Ethiopia and south to Botswana, eastern South Africa and Swaziland (Fig. 1). *E. capensis* has been recorded in dry, Afromontane and riverine forests on well drained and deep

Fig. 1: Distribution of *Ekebergia capensis* in tropical Africa

sandy soils at an altitude ranging from 600 m to 3000 m above sea level and different rainfall regimes ranging from 750 mm to 2000 mm per annum [16]. In the savanna woodland and wooded grassland, *E. capensis* has been recorded on termite mounds [15].

MEDICINAL USES OF *E. CAPENSIS*

The bark, fruits, leaves, roots, stem bark, and wood of *E. capensis* are used as remedies for human and animal diseases (Table 1). Information on medicinal uses of the species has been found in Cameroon, Ethiopia, South Africa, Kenya, Uganda, Nigeria, and Swaziland. Major diseases recorded in at least three countries include fever and malaria, gastrointestinal problems, pain, parasitic worms, reproductive problems in women, respiratory problems, and skin diseases (Fig. 2). In multi-therapeutic applications, the bark maceration of *E. capensis* is mixed with the bark of *Diospyros lycioides* Desf. and taken orally as an herbal medicine for blood in feces [17]. The bark decoction of *E. capensis* is mixed with roots of *Euclea natalensis* A. DC. and taken orally as an herbal medicine for cough, heartburn, and respiratory complaints [18].

PHYTOCHEMICAL AND NUTRITIONAL COMPOSITION OF *E. CAPENSIS*

Several phytochemical compounds and minerals have been identified from leaves, stems, roots, root, and stem bark of *E. capensis* (Table 2). Other phytochemical compounds identified from the bark, leaves, roots, seeds, stem bark, and twigs of *E. capensis* include anthraquinones, flavonoids, glycosides, iridoids, polyphenols, phytosteroids, saponins, tannins, and withanolides [48,55-57]. Total flavonoids, gallotannins, iridoids, phenolics, and condensed tannins content of various parts of *E. capensis* are shown in Table 3. Some of the phytochemical compounds isolated from *E. capensis* demonstrated various biological activities and these include antiplasmodial activities exhibited by compounds 8, 24 [58], 23, 41, and 42 [59], *in vivo* antimalarial activities exhibited by compound 24 [58], cytotoxic activities

Table 1: Medicinal uses of *Ekebergia capensis*

Medicinal use	Parts of the plant used	Country	References
Monotherapeutic applications			
Anthrax infection	Leaves	South Africa	[19]
Blood purifier	Leaves	South Africa	[19]
Blood pressure	Leaves	South Africa	[19]
Cancer (breast, skin, and throat)	Bark, fruits, and leaves	Ethiopia and Kenya	[20,21]
Charms and casting of spells (love charm, protection of homestead and ward off evil spirits)	Bark and stem	South Africa and Swaziland	[22-24]
Disinfectant	Bark	South Africa	[23]
Emetic	Bark and leaves	South Africa and Swaziland	[1,18,23-26]
Epilepsy	Leaves	Nigeria	[27]
Ethnoveterinary medicine	Bark, flowers, fruits, leaves, roots, and stems	Ethiopia and Kenya	[28-32]
Exhaustion	Bark	South Africa	[23]
Fever and malaria	Bark, leaves, roots, and stem bark	Ethiopia, Kenya, Nigeria, and Uganda	[27,33-38]
Gastrointestinal problems (diarrhea, dysentery, gastritis, and stomach ache)	Bark, fruits, leaves, roots, and stem bark	Ethiopia, Kenya, South Africa, Swaziland, and Uganda	[1,21,24-26,36,37-40]
Health tonic	Bark	Kenya	[34]
Heart problems (heartburn and heart problems)	Bark, leaves, and roots	South Africa	[1,12,18,19,23]
Liver complaints	Leaves	South Africa	[19]
Mental problem	Leaves	South Africa	[41]
Reproductive problems (induce labor, infertility, menstrual problems, and ovarian cyst)	Bark, stem bark, and wood	Cameroon, Ethiopia, and South Africa	[23,42-44]
Pain (backache and headache, jaw swelling, and pain)	Bark, leaves, and stems	Ethiopia, Kenya, and South Africa	[1,12,17,24-26,29,32,36,45,46]
Parasitic worms (intestinal worms)	Bark, leaves, and stem bark	Kenya, South Africa, and Swaziland	[1,12,23,24,47]
Respiratory problems (chest pains, cold, cough, respiratory complaints, and runny nose)	Bark, leaves, roots, and stem bark	Ethiopia, Kenya, South Africa, and Swaziland	[1,12,18,23,25,26,29,36,40,47-50]
Skin diseases (abscesses, acne, boils, scabies, and skin rash)	Bark, leaves, and roots	Ethiopia, Kenya, and South Africa	[1,12,25,26,36,41,51-53]
Snakebite	Leaves and roots	Uganda	[37]
Sores	Bark	South Africa	[41]
Venereal diseases	Bark, leaves, and roots	Kenya and South Africa	[25,26,54]
Vermifuge	Leaves	South Africa	[1]
Weight loss	Bark	Ethiopia	[32]
Multi-therapeutic applications			
Blood in feces	Bark maceration taken orally mixed with those of *Diospyros lycioides* Desf.	South Africa	[17]
Cough, heartburn, and respiratory complaints	Bark mixed with roots of *Euclea natalensis* A. DC.	South Africa	[18]

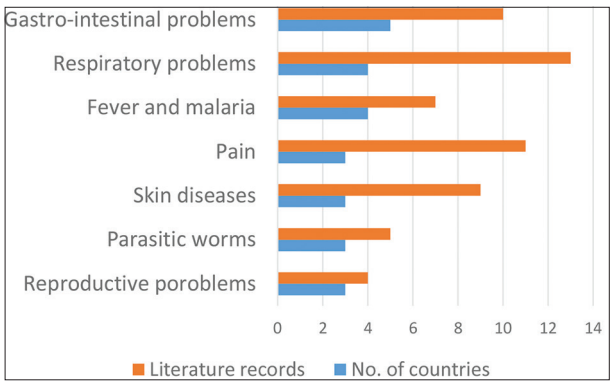

Fig. 2: Diseases treated by *Ekebergia capensis* in tropical Africa

exhibited by compounds 23, 24, 26, and 43 [60], and toxicity activities demonstrated by compounds 9 and 10 [61].

PHARMACOLOGICAL ACTIVITIES OF *E. CAPENSIS*

Some of the pharmacological activities of *E. capensis* listed in literature include acetylcholinesterase-inhibitory [57], analgesic and anti-inflammatory [26,69,70], anthelmintic [55,71], antibacterial [25,51,56,72,73], antigonococcal [25,67], antimycobacterial 74], antimycoplasmal [47], antifungal [25,56,72,73], antihypertensive [19,75], antioxidant [27,57,68,76], antimalarial and antiplasmodial [33,34,58,59,77-79], antischistosomal [80], antitrypanosomal [81], and antiviral [25,60] and cytotoxicity [26,34,59,60,76,82-84] activities. These pharmacological activities of various parts of the species are summarized below.

Acetylcholinesterase inhibitory

Amoo *et al.* [57] evaluated acetylcholinesterase inhibitory properties of *E. capensis* using colorimetric assay with galanthamine at 20 µM as a positive control. Acetylcholinesterase inhibition (%) at 1.0 mg/ml was 73.8%–89.7%.These results suggest that *E. capensis* extracts deserve further investigation as they may provide secondary metabolites which

Table 2: Phytochemical compounds identified from *Ekebergia capensis*

No.	Compound	Method of compound analyzes	Plant part	References
	Alkaloid			
1	Ekeberginine	NMR	Stem bark	[62]
	Coumarins			
2	Ekersenin	NMR	Stem bark	[58,63]
3	4,6-dimethoxy-5-methylcoumarin	NMR	Stem bark	[58]
4	7-hydroxy-6-methoxycoumarin	NMR	Wood	[42]
5	Xanthoxyletin	NMR	Stem bark	[62]
	Glycoflavonoids			
6	Kaempferol-3-O-β-D-glucopyranoside	MS and NMR	Leaves	[59]
7	Quercetin-3-O-β-D-glucopyranoside	MS and NMR	Leaves	[59]
	Limonoids			
8	7-deacetoxy-7-oxogedunin	NMR	Stem bark	[58]
9	Capensolactones l	MS and NMR	Seeds	[61]
10	Capensolactones 2	MS and NMR	Seeds	[61]
11	Capensolactones 3	MS and NMR	Seeds	[61]
12	Ekebergin	NMR	Seeds	[64]
13	Methyl 3x-hydroxy-3-deoxyangolensate	MS and NMR	Seeds	[61]
14	Methylangolensate	NMR	Stem bark	[58]
15	Mexicanolide	NMR	Stem bark	[58]
16	Proceranolide	MS and NMR	Leaves and stem bark	[58,59]
	Phenolic			
17	Atraric acid	NMR	Bark	[65]
	Phytosterol			
18	β-sitosterol	NMR	Bark and wood	[42,65]
19	β-sitosterol oleate	NMR	Bark	[65]
20	β-sitosterol palmitate	NMR	Bark	[65]
	Pregnane			
21	(Z)-volkendousin	NMR	Stem bark	[58]
	Triterpenoids			
22	2,3,22,23-tetrahydroxy-2,6,10,15,19,23-hexamethyl-6,10,14,18-tetracosatetraene	NMR	Bark, stem bark and wood	[42,58,59,66]
23	2-hydroxymethyl-2,3,22,23-tetrahydroxy -6,10,15,19,23 -pentamethyl-6,10,14,18-tetracosatetraene	NMR	Bark and stem bark	[58,59,66]
24	3,11-dioxoolean-12-en-28-oic acid	NMR	Stem bark	[58]
25	3-epi-oleanolic acid	MS and NMR	Bark, root bark, stem bark, and wood	[42,58,59,65,66]
26	3-oxo-12β-hydroxy-oleanan-28,13β-olide	MS and NMR	Root bark and stem bark	[58,59]
27	7-acetylneotrichilenone	NMR	Stem bark	[58]
28	Ekeberins A	MS and NMR	Root bark and stem bark	[58,59]
29	Ekeberins B	NMR	Stem bark	[58]
30	Ekeberins C1	NMR	Stem bark	[58]
31	Ekeberins C2	NMR	Stem bark	[58]
32	Ekeberins C3	NMR	Stem bark	[58]
33	Ekeberins D1	NMR	Stem bark	[58]
34	Ekeberins D2	NMR	Stem bark	[58]
35	Ekeberins D3	NMR	Stem bark	[58]
36	Ekeberins D4	NMR	Stem bark	[58]
37	Ekeberins D5	NMR	Stem bark	[58]
38	Lupeol	NMR	Bark	[65]
39	Melliferone	NMR	Stem bark	[58]
40	Oleanolic acid	NMR	Bark and stem bark	[58,66]
41	Oleanolic acid	MS and NMR	Bark, root bark, and stem bark	[58,59,66]
42	Oleanolic acid	MS and NMR	Bark, root bark, stem bark, and wood	[42,58,59,65,66]
43	Swietenolide	NMR	Stem bark	[58]

Table 3: Total flavonoids, gallotannins, iridoids, phenolics, and condensed tannins content of *Ekebergia capensis*

Phytochemical composition	Values	Plant parts	References
Condensed tannins (% leukocyanidin equivalents)	0.32–0.47	Bark and leaves	[25]
Flavonoids (μg catechin equivalents/g dry weight)	1.48–4.84	Bark and leaves	[25]
Gallotannin (μg gallic acid equivalents/g dry weight)	35.37–70.00	Bark and leaves	[25]
Total condensed tannins (mg cyanidin chloride equivalents/g dry weight)	12.5	Leaf	[67]
Total flavonoids (mg catechin equivalent/g dry weight)	22.8-–26.8	Leaf	[57,67]
Total iridoids (μg harpagoside equivalents/g dry weight)	547.6–2221.5	Leaves and twigs	[57]
Total phenolics (mg gallic acid equivalents/g dry weight)	9.63–45.0	Brak, leaves and twigs	[25,57,67,68]

can act as natural acetylcholinesterase inhibitors required for the treatment of neurodegenerative disorders.

Analgesic and anti-inflammatory

William *et al*. [70] evaluated the analgesic activities of aqueous stem bark extracts of *E. capensis* in albino rats using a hot plate and tail immersion tests. Rats were administered with doses of 100 mg/kg and 200 mg/kg intraperitoneally, and a standard drug pentazocine 10 mg/kg was used. The extract showed activities which were dose-dependent, and the activities were comparable to that of pentazocine in the hot plate method but higher than pentazocine in the tail immersion method. At the dosage of 200 mg/kg body weight, the latency period increased from 21.4 min at pre-treatment to 48.2 min and 59.4 min and 15 min and 30 min post-treatment, respectively. The result of extract on tail immersion test response showed that there were no significant changes in the time for tail withdrawal at all dosages of extract administered except at 100 mg/kg body weight and 200 mg/kg body weight where the time for tail withdrawal was significantly shorter than that of the pre-treatment [70]. Comparing reaction times obtained for animals treated with the extracts and the control values, it was apparent that the extracts caused prolongation of latency times, which is indicative of centrally mediated activity.

Jäger *et al*. [69] evaluated aqueous and ethanolic root extracts of *E. capensis* in an *in vitro* assay for cyclooxygenase (COX) inhibitors with indomethacin (0.5 µg) as the control. The ethanolic extract of *E. capens is* showed inhibition of 82% which was >66.5% inhibition exhibited by the indomethacin control. Based on these results, the RE might be a rationale for the ethnopharmacological claim that *E. capensis* possess anti-inflammatory properties. Mulaudzi *et al*. [26] evaluated the anti-inflammatory activities of dichloromethane, ethanol, petroleum ether, and water bark, and leaf extracts of *E. capensis* against the COX (COX-1 and COX-2) enzymes. All the solvent extracts showed moderate to high (40–90%) inhibition activity toward COX-1, and insignificant to high (<20–85%) inhibition activity toward COX-2 at 250 µg/ml and three further concentrations were evaluated at 31.25 µg/ml, 62.5 µg/ml, and 125 µg/ml to determine inhibitory concentration (IC_{50}) values. Water bark extracts bark showed half maximal IC_{50} value of 0.01 µg/ml and 0.05 µg/ml toward COX-1 and COX-2, respectively [26]. These results support the traditional use of *E. capensis* in managing inflammatory ailments and diseases such as abscesses and acne in South Africa [1,41,51,52], pain and swelling of jaws in Ethiopia [32,46], and sores in South Africa [41].

Anthelmintic

McGaw *et al*. [71] evaluated anthelmintic activities of hexane, ethanol and waterleaf extracts of *E. capensis* on the mortality and reproductive ability of the free-living nematode *Caenorhabditis elegans* in two different assays. All extracts exhibited activities at a concentration of 2 mg/ml after the 7 day incubation period, with only water and ethanol extracts showing activities at a concentration of 1 mg/ml and after 2 h incubation period, respectively [71]. Eguale *et al*. [55] evaluated anthelmintic activities of crude aqueous and hydroalcoholic extracts of the seeds of *E. capensis* on eggs and adult *Haemonchus contortus*. Both aqueous and hydroalcoholic extracts induced significant egg hatching inhibition with aqueous extract requiring maximum concentration of 0.25mg/ml to induce 100% egg hatch inhibition while the hydroalcoholic extracts did not induce complete inhibition at the highest concentration tested of 2mg/ml. The aqueous extract induced 50% inhibition (ED_{50}) at 0.06 mg/ml while the ED_{50} value of hydroalcoholic extract was 1.03mg/ml. After 24 h of exposure of adult *H. contortus* to different concentrations of plant extracts, hydroalcoholic extracts produced motility or mortality of adult *H. contortus* to the level of 60% at a concentration of 8mg/ml while aqueous extract produced only 43.3% at the same concentration [55]. These findings are comparable to the standard, albendazole which killed the parasites in a dose-dependent manner, and all the worms were dead at a concentration of 0.5 mg/ml within 24 h [55]. These biological evaluations are of importance in the traditional use of *E. capensis* as herbal medicine against intestinal worms in Kenya, South Africa, and Swaziland [1,12,23,24,47].

Antibacterial

Rabe and Van Staden [51] evaluated antibacterial activities of water and methanol bark extracts of *E. capensis* against *Staphylococcus aureus, Staphylococcus epidermis, Bacillus subtilis, Escherichia coli,* and *Klebsiella pneumoniae* using the agar diffusion and dilution methods with neomycin as the positive control. The extracts showed activities against *S. aureus, S. epidermis,* and *B. subtilis* with minimum inhibition concentration (MIC) values ranging from 2.0 mg/ml to 4.0 mg/ml [51]. Ndukwe *et al*. [56] evaluated the antibacterial activities of methanol leaf, root, and stem bark extracts of *E. capensis* against *B. subtilis, E. coli, Klebsiella, Pseudomonas, Salmonella typhi,* and *S. aureus* using disc diffusion assay. The extracts showed activities with a zone of inhibition ranging from 5 mm to 23 mm and MIC value of 6.25 µg/ml [56]. Mulaudzi *et al*. [25] investigated the antibacterial effects of aqueous, acetone, dichloromethane, ethanol, methanol, and petroleum ether bark and leaf extracts of *E. capensis* against *B. subtilis, E. coli, K. pneumoniae,* and *S. aureus* using microdilution bioassay with neomycin as the positive control. The minimal microbicidal concentration (MMC) of the tested bacteria ranged from 0.39 mg/mL to 3.13 mg/mL [25]. Similarly, York *et al*. [72] assessed the antibacterial properties of aqueous and dichloromethane-methanol (1:1) leaf extracts of *E. capensis* against *K. pneumoniae, Moraxella catarrhalis, Mycobacterium smegmatis,* and *S. aureus* using microdilution assay with ciprofloxacin as the positive control. The extract showed activities with MIC values ranging from 1.33 mg/ml to 16.0 mg/ml [72]. Mabona *et al*. [73] evaluated antibacterial activities of aqueous and dichlomethane-methanol (1:1) bark and leaf extracts of *E. capensis* using the microtiter plate dilution technique against dermatologically relevant pathogens such as *Brevibacillus agri, Propionibacterium acnes, Pseudomonas aeruginosa, S. aureus,* and *S. epidermidis* with ciprofloxacin as the positive control and acetone and dimethyl sulfoxide (DMSO) as negative controls. The extracts showed activities with MIC values ranging from 0.38 mg/mL to >16.00 mg/mL [73]. These antibacterial activities displayed by different extracts of *E. capensis* somehow confirm the species' antibacterial potential and its usefulness in the treatment and management of bacterial infections such as boils in South Africa [1,41,51,52], diarrhea in Kenya and Uganda [36,37], dysentery in South Africa [25,26], stomach problems in Ethiopia [21,39], and venereal diseases in Kenya and South Africa [25,26,54].

Antigonococcal

Mulaudzi *et al*. [25] evaluated the antigonococcal activities of aqueous, acetone, dichloromethane, ethanol, methanol, and petroleum ether bark and leaf extracts of *E. capensis* against *Neisseria gonorrhoeae* through determination of clear zones of inhibition with ciprofloxacin and DMSO as positive and negative controls, respectively. *E. capensis* showed moderate to high activity with dichloromethane, ethanol, and petroleum ether extracts with percentage inhibition ranging from 45.0% to 96.0% [25]. Similarly, Vambe *et al*. [67] evaluated the antigonococcal activities of dichloromethane, methanol, and petroleum ether and waterleaf extracts of *E. capensis* against *N. gonorrhoeae* using microdilution and agar disk diffusion techniques with ciprofloxacin as the positive control. All extracts exhibited activities with MIC value of >2.5 mg/ml. The good antigonococcal activities exhibited by *E. capensis* extracts tested in this study could lead to the isolation of lead antigonococcal compounds.

Antimycobacterial

Lall and Meyer [74] evaluated antimycobacterial activities of acetone extract of *E. capensis* against a drug-sensitive strain of *Mycobacterium tuberculosis* (H37Rv) using the agar plate method. The activity of the extract was 0.5 mg/ml, and further evaluation was carried out using a rapid radiometric method to confirm the inhibitory activity. The extract exhibited MIC value of 0.1 mg/ml against the H37Rv strain. These antimycobacterial activities suggest that *E. capensis* extracts deserve further investigation as they may provide secondary metabolites which may lead to tuberculosis drug discovery.

Antimycoplasmal

Kama-Kama *et al*. [47] evaluated antimycoplasmal activities of methanol-dichloromethane (1:1) and methanol stem bark extracts of *E. capensis* against *Mycoplasma mycoides* subsp. capri, five strains of *M. mycoides* subsp. *mycoides* and one strain of *Mycoplasma capricolum* subsp. *Capricolum* using broth microdilution assays. All the extracts showed activities with MIC values ranging from 0.13 mg/ml to 0.15 mg/ml [47]. These findings suggest that *E. capensis* contains phytochemical compounds that might be useful for the treatment and management of respiratory diseases in ruminants.

Antifungal

Ndukwe *et al*. [56] evaluated the antifungal activities of methanol leaf, root, and stem bark extracts of *E. capensis* against *Aspergillus niger* and *Candida albicans* using disc diffusion assay. The extracts showed activities with a zone of inhibition ranging from 5 mm to 20 mm [56]. Mulaudzi *et al*. [25] evaluated the antifungal effects of aqueous, acetone, dichloromethane, ethanol, methanol, and petroleum ether bark and leaf extracts of *E. capensis* against *C. albicans* using microdilution bioassay with amphotericin as the positive control. The MIC value of the tested fungus ranged from 0.39 mg/mL to 6.3 mg/mL, while the minimum fungicidal concentration values ranged from 3.13 mg/mL to 12.5 mg/mL [25]. Similarly, York *et al*. [72] assessed antifungal properties of aqueous and dichloromethane-methanol (1:1) leaf extracts of *E. capensis* against *Cryptococcus neoformans* using microdilution assay with amphotericin B as the positive control. The dichloromethane-methanol (1:1) extract demonstrated the best activity with MIC value of 0.40 mg/ml, while aqueous extract exhibited activities with MIC value of 16.0 mg/ml [72]. Mabona *et al*. [73] evaluated antifungal activities of aqueous and dichlomethane-methanol (1:1) bark and leaf extracts of *E. capensis* using the microtiter plate dilution technique against dermatologically relevant pathogens such as *C. albicans, Microsporum canis,* and *Trichophyton mentagrophytes* with amphotericin B as the positive control and acetone and DMSO as negative controls. The extracts showed activities with MIC values ranging from 1.0 mg/mL to 16.00 mg/mL and noteworthy antifungal activities were displayed by dichlomethane-methanol bark extracts against *C. albicans, M. canis,* and *T. mentagrophytes* with MIC value of 1.0 mg/mL [73].

Antihypertensive

Duncan *et al*. [19] evaluated antihypertensive properties of ethanol and waterleaf extracts of *E. capensis* using the angiotensin-converting enzyme (ACE) assay. The water and ethanol extracts exhibited ACE inhibition rate of 26% and 37%, respectively [19]. Kamadyaapa *et al*. [75] evaluated the *in vivo* effects of *E. capensis* leaf ethanolic extracts on the blood pressure of anesthetized normotensive male Wistar rats and conscious weanling Dahl salt-sensitive (DSS) rats, which develop hypertension as they age. The authors assessed contractile or relaxant responses to extracts in the absence or presence of reference drugs in Wistar rat isolated aortic rings precontracted with methoxamine hydrochloride (10 μM). The extracts prevented the development of hypertension in weanling genetically hypertensive DSS rats and the *in vivo* reduction in blood pressure by the extract occurred without significant alterations in the heart rate, suggesting that the *in vitro* cardiovascular effects of the extract significantly contributed to the hypotensive effects. These findings showed that the hypotensive effect of the extract was in part mediated through modulation of total peripheral resistance of the vascular smooth muscles, as evidenced by the extract's elicited dose-dependent vasorelaxations in endothelium-intact and endothelium-denuded aortic ring preparations [75].

Antioxidant

Sofidiya *et al*. [68] evaluated antioxidant activities of leaf extracts of *E. capensis* using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging and reducing power assays. The extract showed a dose-dependent increase in activities ranging from 81.0% to 96.5% inhibition on DPPH which was comparable to the activities of the reference α-tocopherol which showed 96.9%–97.9% inhibition on DPPH. Reducing power results of the extracts were also dose-dependent and comparable to the activities exhibited by the reference α-tocopherol [68]. Aladesanmi *et al*. [27] evaluated antioxidant activities of methanol leaf extracts of *E. capensis* using the DPPH free radical scavenging assay. The extract exhibited activities with half maximal effective concentration (EC_{50}) value of 13.3 μg/ml which was comparable to EC_{50} value of 14.2 μg/ml exhibited by rutin, a pure standard antioxidant compound [27]. Amoo *et al*. [57] evaluated the antioxidant activities of *E. capensis* using the DPPH free radical scavenging and β-carotene-linoleic acid model assays after long-term storage in comparison with freshly collected materials. The extracts showed EC_{50} values of 4.7 μg/ml–25.5 μg/ml [57]. Tagne *et al*. [76] evaluated the antioxidant activities of methanol bark extracts of *E. capensis* using the DPPH and nitric oxide radical scavenging assays. The extract showed activities with DPPH and nitric oxide exhibiting an IC_{50} value of 15.8 μg/mL and 299μg/mL which was comparable to IC_{50} values of 22.7 μg/mL and 108 μg/mL exhibited by the standard gallic acid and ascorbic acid, respectively. Tagne *et al*. [76] also evaluated the antioxidant activities of hexane, dichloromethane, ethyl acetate, butanol, and methanol bark extracts of *E. capensis* using DPPH radical scavenging assay. Hexane extracts showed no activity, while dichloromethane showed weak activity with an IC_{50} value of 366.6 μg/mL and ethyl acetate, butanol and methanol were active with IC_{50} values ranging from 14.0 μg/mL to 20.2 μg/mL [76].

Antimalarial and antiplasmodial

Clarkson *et al*. [77] evaluated antiplasmodial activities of *E. capensis* aqueous, dichloromethane, dichloromethane-methanol (1:1) fruit and twig extracts against *Plasmodium falciparum* using the parasite lactate dehydrogenase assay. The dichloromethane-methanol (1:1) fruit extract showed promising activity while dichloromethane-methanol (1:1) twig extract showed weak activity with IC_{50} values of 10 μg/mL and 18 μg/mL, respectively [77]. Muregi *et al*. [33] evaluated antiplasmodial activities of chloroform, ethyl acetate, and hexane and methanol leaf extracts of *E. capensis* using the [$G^{-3}H$] hypoxanthine incorporation assay using chloroquine sensitive and resistant laboratory-adapted strains of *P. falciparum* as the test organism. The hexane extract exhibited no antiplasmodial activity, but chloroform, ethyl acetate, methanol, and water extracts gave good IC_{50} values (<5 μg/mL) suggesting that *E. capensis*has a high *in vitro* antiplasmodial activities. Murata *et al*. [58] evaluated antiplasmodial activities of compounds 8, 22, 23, 33, 34, 35, 36, and 37 isolated from the stem bark of *E. capensis* against the chloroquine sensitive strain of *P. falciparum*. The compounds 8 and 23 showed activities with IC_{50} values of 6 μM and 7 μM, respectively [58]. Irungu *et al*. [59] evaluated antiplasmodial activities of leaf and root extracts of *E. capensis* and compounds isolated from the species against the chloroquine sensitive (D6) and the chloroquine-resistant (W2) strains of *P. falciparum*. The leaf and root extracts, as well as compounds 22, 23, 41, and 42 exhibited moderate activities against the D6 and W2 strains of *P. falciparum* with IC_{50} values ranging from 18.2 μM to 82.7 μM [59].

Koch *et al*. [34] evaluated antimalarial activities of bark extracts of *E. capensis* against a chloroquine-sensitive (D6) strain of *P. falciparum* using a semiautomated microdilution technique. The extract showed activity with an IC_{50} value of 3.97 μg/ml. Muregi *et al*. [78] evaluated *in vivo* antimalarial activities of leaf, root, and stem bark extracts of *E. capensis* in mice against a chloroquine-tolerant *Plasmodium berghei* NK65, either alone or in combination with chloroquine. The extracts showed activities with parasitemia suppressions ranging from 14.8% to 33.3% when extract used alone and 37.9% to 59.1% when the extract is used in combination with chloroquine. The extracts gave a 20.0–40.0% mouse survival when used alone and 20.0–75.0% when the extract is used in combination with chloroquine. In combination with chloroquine, the extracts showed better chemo-suppression as well as longer mouse survival suggesting synergistic interactions of the extract and chloroquine [78]. Chukwuma [79] evaluated toxicity of hexane and methanol leaf extracts of *E. capensis* by exposing the fourth instar larvae of *Anopheles gambiae* to different extract concentrations of 62.5 μg/mL to 1000 μg/mL using N,N-diethyl-3-methylbenzamide as a reference

insecticide. The hexane fraction displayed mortality at 0.63 mg/mL with LC_{50} value of 0.81 mg/mL which was comparable to the LC_{50} value of 1.1 mg/mL exhibited by N,N-diethyl-3-methylbenzamide, a reference insecticide [79]. Murata *et al*. [58] evaluated *in vivo* antimalarial activities of compounds 22 and 23 isolated from the stem bark of *E. capensis* in mice against artificially induced chloroquine-sensitive *P. berghei* NK 65 using the 4-day suppressive protocol. Each mouse within a group received test compound at a dose of 100, 250, and 500 mg/kg body weight, once a day for 4 days using a metal catheter. The introduced group received a corresponding volume of distilled water. The compound 23 at a dose of 500 mg/kg showed moderate parasitemia suppression of 52.9% against *P. berghei* NK 65 in a mouse model [58]. Therefore, *E. capensis* extracts showed promising antimalarial and antiplasmodial activities and these findings corroborate the traditional usage of bark, leaves, roots, and stem bark as remedies against malaria in Ethiopia [38], Kenya [33-35], Nigeria [27], and Uganda [37].

Antischistosomal

Musili *et al*. [80] evaluated antischistosomal activities of aqueous leaf extracts of *E. capensis* against juvenile, immature adult, and adult worms of *Schistosoma mansoni* in infected Swiss albino mice. The mice were infected with 90 cercariae each and treated orally with varying doses of aqueous extracts of *E. capensis* at doses of 25 mg/kg, 50 mg/kg, 100 mg/kg, 200 mg/kg, and 400 mg/kg at 2 weeks (juvenile worms), 4 weeks (immature worms), and 7 weeks (adult worms) post-infection with praziquantel (PZQ) and artemether as positive controls while infected untreated group was used as negative controls [80]. The extracts showed significant dose-dependent percentage worm load reduction at different doses ranging from 100 mg/kg to 400 mg/kg and the extracts also significantly reduced liver and intestine egg load counts at doses ranging from 50 mg/kg to 400 mg/kg which was also dose-dependent. These observed activities on both adult and juvenile worms of the parasite were comparable to results obtained using positive control drugs PZQ and artemether [80]. A similar trend was exhibited by PZQ and artemether as positive controls these findings show the potential use of *E. capensis* in the management of schistosomiasis.

Antitrypanosomal

Mokoka *et al*. [81] evaluated antitrypanosomal activities of dichloromethane-methanol root extracts of *E. capensis* against *Trypanosoma brucei rhodesiense* using serial dilution. The extract exhibited activity with IC_{50}value of 1.36 µg/mL with a moderate selectivity index value of 24.3, indicating its selectivity towards killing the parasites with very little toxicity towards the myoblasts L-6 cells with an IC_{50} value of 33.0 µg/mL [81].

Antiviral

Bagla *et al*. [60] evaluated antiviral activities of hexane, dichloromethane, and methanol root extracts of *E. capensis* against canine distemper virus, canine parainfluenza virus-2, feline herpesvirus-1, and lumpy skin disease virus using virucidal and attachment assays. Dichloromethane and hexane extracts inhibited all viruses by at least 50%, and the extracts showed weak activities with EC_{50} values ranging from 30.9 µg/ml to 78.2 µg/ml with selectivity index values of <1 [60]. Mulaudzi *et al*. [25] evaluated anti-HIV activities of aqueous and methanol bark and leaf extracts of *E. capensis* using a non-radioactive HIV-1 reverse transcriptase (RT) colorimetric ELISA kit. The aqueous bark and leaf extracts as well as methanol leaf extract showed good HIV-1 RT inhibition percentage (70%) at 1 mg/mL based on COX-assay, with bark and leaf water extracts exhibiting dose-dependent IC_{50} values of 0.01±0.00 mg/mL while leaf methanol extract exhibited IC_{50} values of 0.39±0.06 mg/mL [25].

Cytotoxicity

Tagne *et al*. [76] evaluated antiproliferative activities of methanol bark extracts of *E. capensis* on four cell line panels consisting of NCI-H460 (lung cancer), MCF7 (breast cancer), PC3 (prostate cancer), HeLa (cervix cancer cell), and normal cell 3T3 (mouse cervical cells) using the sulforhodamine-B assay. The extracts showed activity with half-maximal growth inhibition (GI_{50}) values ranging from 13.5 µg/mL to 28.8 µg/mL which were comparable to GI_{50} values of 0.02 µg/mL–0.70 µg/mL exhibited by the positive control doxorubicin [76]. Tagne *et al*. [76] evaluated antiproliferative activities of hexane, dichloromethane, ethyl acetate, butanol, and methanol bark extracts of *E. capensis* against NCI-H460, MCF7, and 3T3 using the sulforhodamine-B assay. The extracts exhibited activities with GI_{50} values ranging from 10.0 µg/mL to 52.0 µg/mL [76]. Elgorashi *et al*. [82] evaluated genotoxic activities of dichloromethane bark extract of *E. capensis* using the Ames assay with *S. typhimurium* strain TA98 and TA100, and VITOTOX® tests with and without metabolic activation. No genotoxic effects were demonstrated by the extracts. Taylor *et al*. [83] evaluated genotoxic activities of dichloromethane and methanol leaf extract of *E. capensis* using the cytochalasin B micronucleus test and alkaline comet assay in human white blood cells. The extract showed clastogenic and/or aneuploid activity although micronucleus frequencies were well below that found for the positive control mitomycin at 0.1 µg/mL. Reid *et al*. [84] evaluated mutagenic and antimutagenic activities of dichloromethane and methanol bark extract of *E. capensis* using the *Salmonella* or microsome mutagenicity assay (Ames) against *S. typhimurium* TA98 and TA100 bacterial strains in the presence and absence of metabolic activator S9. No mutagenic and antimutagenic effects were demonstrated by the extracts. Koch *et al*. [34] evaluated cytotoxicity activities of bark extracts of *E. capensis* using KB human oral epidermoid cancer cell line with vinblastine (median effective dose [ED_{50}]=0.04 µg/ml). The extract lacked toxicity to KB cells with ED_{50} value >20.0 µg/ml and selectivity index value >5.1. Bagla *et al*. [60] evaluated the cytotoxicity activities of hexane, dichloromethane, acetone, and methanol root extracts of *E. capensis* using a colorimetric tetrazolium-based 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Dichloromethane and hexane showed activities with half-maximal cytotoxic concentration (CC_{50}) values ranging from 2.5 µg/ml to 43.1 µg/ml with selectivity index values of <1. Mulaudzi *et al*. [26] evaluated genotoxicity activities of dichloromethane, ethanol, petroleum ether, and water bark and leaf extracts of *E. capensis* using the Ames test, with and without S9 (metabolic activation) against *S. typhimurium* tester strain TA98. The Ames test revealed that all leaf extracts were non-mutagenic toward *S. typhimurium* strain TA98 but bark extracts induced 50.0 revertant colonies at 500 µg/ml and 50.0 µg/ml and there was no dose-dependent increase and; therefore, the extract could be classified as a weak mutagen [26]. Irungu *et al*. [59] evaluated the cytotoxicity activities of leaf and root extracts of *E. capensis* and compounds 6, 7, 16, 22, 23, 25, 28, 41, and 42isolated from the species against the mammalian African monkey kidney (vero), mouse breast cancer (4T1), human larynx carcinoma (HEp2), and human breast cancer (MDA-MB-231) cell lines using MTT assay. The leaf and root extracts exhibited activities against vero, 4T1 and HEp2 with IC_{50} values ranging from 2.8 µM to 97.8 µM while compounds 42, 25, 23, and 22 showed activities with compound 42 with the highest cytotoxicity with IC_{50} values of 1.4 µM and 13.3 µM against the HEp2 and 4T1 cells, respectively [59].

Uterotonic

Sewram *et al*. [42] evaluated the uterotonic activities of aqueous wood extracts of *E. capensis* using both pregnant and non-pregnant guinea pig uterine smooth muscle *in vitro*. The extract exhibited positive uterotonic activities. Sewram *et al*. [42] evaluated the uterotonic activities of compounds 25 and 42 isolated from *E. capensis* using both pregnant and non-pregnant guinea pig uterine smooth muscle *in vitro*. The results of this study show that compounds 25 and 42 possess varying degrees of agonist activity on uterine smooth muscle with minor changes in the molecular structure affecting its intrinsic activity on uterine muscle. The compound 25 was observed to mediate its effect through the cholinergic receptor [42].

Toxicity

Mulholland and Lourine [61] evaluated toxicity activities of hexane seed extract of *E. capensis* as well as compounds 9, 10, 11, and 13 isolated from the seeds of using the brine shrimps lethality test. The

extracts at a concentration of 10 µg/ml, 100 µg/ml, and 1000 µg/ml, compounds 9 and 10 demonstrated moderate activities of 10% at the lowest concentration and 61%–80% at the highest concentration [61]. Based on these toxicity evaluations, it can be inferred that *E. capensis* has some potential toxicity and caution should be exercised when using the species as herbal medicine. These findings corroborate the traditional use of the species as a fish poison in DRC and Nigeria [5].

CONCLUSION

The present review summarizes the ethnomedicinal uses, phytochemistry, pharmacology, and toxicity of different extracts and compounds of *E. capensis*, one of several medicinal plants in tropical Africa [85,86]. Several phytochemical compounds including alkaloids, anthraquinones, coumarins, flavonoids, glycoflavonoids, glycosides, iridoids, limonoids, polyphenols, phytosteroids, pregnane, saponins, tannins, and withanoides have been identified from different plant parts of the species. In the past 20 years, research on *E. capensis* focused on evaluating acetylcholinesterase-inhibitory, analgesic and anti-inflammatory, anthelmintic, antibacterial, antifungal, antigonococcal, antimycobacterial, antimalarial and antimycoplasmal, antihypertensive, antioxidant, antiplasmodial, antiproliferative, antischistosomal, antitrypanosomal, antiviral and cytotoxicity activities of the different extracts, and compounds isolated from the species. However, there is not yet enough phytochemical and pharmacological data and clinical research on the majority of ethnomedicinal applications of the species. As revealed by the present review, the vast majority of the documented ethnopharmacological studies reported are *in vitro*. There is no doubt that these ethnopharmacological studies demonstrated a remarkable potential of *E. capensis* in the treatment of different human health problems. However, there are limitations associated with the *in vitro* studies. Therefore, future studies on the species should focus on the mechanism of action of the extracts as well as compounds isolated from the species, *in vivo* studies and evaluations of target-organ toxicity. Since *E. capensis* is also used in combination with other plant species in various herbal concoctions, there is a need for extensive research to evaluate synergistic effects of the different extracts or pure isolates to evaluate their ability to enhance the efficiency of the additive mixtures. There is no doubt that *E. capensis* is a valuable medicinal plant characterized by several phytochemical compounds and pharmacological activities; however, future clinical trials are necessary to clinically support the safety and efficacy of the concoctions prepared from the species.

ACKNOWLEDGMENTS

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

AUTHORS' CONTRIBUTIONS

The authors declare that this work was done by the author named in this article.

CONFLICTS OF INTEREST

No conflicts of interest are associated with this work.

REFERENCES

1. Van Wyk BE, Van Oudtshoorn B, Gericke N. Medicinal Plants of South Africa. Pretoria: Briza Publications; 2013.
2. George J, Laing MD, Drewes SE. Phytochemical research in South Africa. S Afr J Sci 2001;97:93-105.
3. Williams VL, Balkwill K, Witkowski ET. A lexicon of plants traded in the Witwatersrand umuthi shops, South Africa. Bothalia 2001;31:71-98.
4. Cunningham AB. African Medicinal Plants: Setting Priorities at the Interface between Conservation and Primary Health Care. Paris: People and Plants Working Paper 1, UNESCO; 1993.
5. Neuwinger HD. Plants used for poison fishing in tropical Africa. Toxicon 2004;44:417-30.
6. Pennington TD, Edwards KS. Meliaceae. In: Berry PE, Yatskievych K, Holst BK, editors. Flora of the Venezuelan Guayana
6. Liliaceae-Myrsinaceae. St. Louis: Missouri Botanical Garden; 2001. p. 528-49.
7. Muellner AN, Samuel R, Chase MW, Coleman A. An evaluation of tribes and generic relationships in Melioideae (*Meliaceae*) based on nuclear ITS ribosomal DNA. Taxon 2008;57:98-108.
8. International Union for Conservation of Nature (IUCN), Meliaceae: 2018 IUCN Red List of Threatened Species (2018). Available from: http://www.iucnredlist.org/search. [Last accessed on 2018 Jan 12].
9. Louppe D, Oteng-Amoako AA, Brink M. Plant resources of tropical Africa 7: Timbers 1. Leiden: PROTA Foundation, Backhuys Publishers; 2008.
10. Atawodi SE, Atawodi JC. *Azadirachta indica* (neem): A plant of multiple biological and pharmacological activities. Phytochem Rev 2009;8:601-20.
11. Palmer E, Pitman P. Trees for Southern Africa Covering All Known Indigenous Species in Republic of South Africa, South West Africa, Botswana, Lesotho and Swaziland. Cape Town: A.A. Balkema; 1972.
12. Schmidt E, Lotter M, McCleland W. Trees and shrubs of Mpumalanga and Kruger National Park. Johannesburg: Jacana Media; 2002.
13. Pennington TD, Styles BT. A generic monograph of the Meliaceae. Blumea 1975;22:419-540.
14. Hyde M, Wursten B, Ballings P, Palgrave MC. Flora of Zimbabwe: Species Information: *Ekebergia capensis* Sparrm. (2018). Available from: https://www.zimbabweflora.co.zw/speciesdata/species.php?species_ id=133540. [Last accessed on 2018 Apr 15].
15. Palgrave MC. Keith Coates Palgrave Trees of Southern Africa. Cape Town: Struik Publishers; 2002.
16. Mairura FS. *Ekebergia capensis* Sparrm. In: Louppe D, Oteng-Amoako AA, Brink M, editors. Plant Resources of Tropical Africa 7: Timbers 1. Leiden: PROTA Foundation, Backhuys Publishers; 2008. p. 227-31.
17. Arnold HJ, Gulumian M. Pharmacopoeia of traditional medicine in Venda. J Ethnopharmacol 1984;12:35-74.
18. Bryant AT. Zulu Medicine and Medicine-Men. Cape Town: C. Struik Publishers; 1966.
19. Duncan AC, Jäger AK, van Staden J. Screening of Zulu medicinal plants for angiotensin converting enzyme (ACE) inhibitors. J Ethnopharmacol 1999;68:63-70.
20. Ochwang'i DO, Kimwele CN, Oduma JA, Gathumbi PK, Mbaria JM, Kiama SG. Medicinal plants used in treatment and management of cancer in Kakamega County, Kenya. J Ethnopharmacol 2014;151:1040-55.
21. Tuasha N, Petros B, Asfaw Z. Medicinal plants used by traditional healers to treat malignancies and other human ailments in Dalle District, Sidama zone, Ethiopia. J Ethnobiol Ethnomed 2018;14:15.
22. Gerstner J. A preliminary checklist of Zulu names of plants with short notes. Bantu Stud 1941;15:277-301.
23. Hutchings A, Scott AH, Lewis G, Cunningham AB. Zulu Medicinal Plants: An Inventory. Pietermaritzburg: University of Natal Press; 1996.
24. Long C. Swaziland's Flora: SiSwati names and uses (2005). Swaziland National Trust Commission, Mbambane. Available from: http://www.sntc.org.sz/index.asp. [Last accessed on 2018 May 7].
25. Mulaudzi RB, Ndhlala AR, Kulkarni MG, Finnie JF, Van Staden J. Antimicrobial properties and phenolic contents of medicinal plants used by the Venda people for conditions related to venereal diseases. J Ethnopharmacol 2011;135:330-7.
26. Mulaudzi RB, Ndhlala AR, Kulkarni MG, Finnie JF, Van Staden J. Anti-inflammatory and mutagenic evaluation of medicinal plants used by Venda people against venereal and related diseases. J Ethnopharmacol 2013;146:173-9.
27. Aladesanmi AJ, Iwalewa EO, Adebajo AC, Akinkunmi EO, Taiwo BJ, Olorunmola FO, *et al*. Antimicrobial and antioxidant activities of some Nigerian medicinal plants. Afr J Tradit Complement Altern Med 2007;4:173-84.
28. Njoroge GN, Bussmann RW. Herbal usage and informant consensus in ethno veterinary management of cattle diseases among the Kikuyus (Central Kenya). J Ethnopharmacol 2006;108:332-9.
29. Okello SV, Nyunja RO, Netondo GW, Onyango JC. Ethno botanical study of medicinal plants used by Sabaots of Mt. Elgon, Kenya. Afr J Tradit Complement Altern Med 2010;7:1-10.
30. Wanzala W, Takken W, Mukabana WR, Pala AO, Hassanali A. Ethno knowledge of Bukusu community on livestock tick prevention and control in Bungoma District, Western Kenya. J Ethnopharmacol 2012;140:298-324.
31. Tekle Y. An ethno-veterinary botanical survey of medicinal plants in Kochore District of Gedeo Zone, Southern nations nationalities and peoples regional state (SNNPRs), Ethiopia. J Sci Innovative Res

2014;3:433-45.
32. Kewessa G, Abebe T, Demessie A. Indigenous knowledge on the use and management of medicinal trees and shrubs in Dale district, Sidama zone, Southern Ethiopia. Ethnobot Res Appl 2015;14:171-82.
33. Muregi FW, Chhabra SC, Njagi EN, Lang'at-Thoruwa CC, Njue WM, Orago AS, *et al*. Anti-plasmodial activity of some Kenyan medicinal plant extracts singly and in combination with chloroquine. Phytother Res 2004;18:379-84.
34. Koch A, Tamez P, Pezzuto J, Soejarto D. Evaluation of plants used for antimalarial treatment by the maasai of Kenya. J Ethnopharmacol 2005;101:95-9.
35. Njoroge GN, Bussmann RW. Diversity and utilization of antimalarial ethnophytotherapeutic remedies among the Kikuyus (Central Kenya). J Ethnobiol Ethnomed 2006;2:8.
36. Gachathi M. Kikuyu Botanical Dictionary: A Guide to Plant Names, Uses and Culture Values. Nairobi: Tropical Botany Press; 2007.
37. Opio DR, Andama E, Kureh GT. Ethnobotanical survey of antimalarial plants in areas of Abukamola, Angeta, Oculokori and Omarari of Alebtong District in Northern Uganda. Eur J Med Plants 2017;21:1-14.
38. Suleman S, Tufa TB, Kebebe D, Belew S, Mekonnen Y, Gashe F, *et al*. Treatment of malaria and related symptoms using traditional herbal medicine in Ethiopia. J Ethnopharmacol 2018;213:262-79.
39. Regassa R. Assessment of indigenous knowledge of medicinal plant practice and mode of service delivery in Hawassa city, Southern Ethiopia. J Med Plant Res 2013;7:517-35.
40. Meragiaw M, Asfaw Z, Argaw M. The status of ethnobotanical knowledge of medicinal plants and the impacts of resettlement in Delanta, North Western Wello, Northern Ethiopia. Evid Based Complement Alternat Med 2016;2016:24.
41. Pujol J. Natur Africa: The herbalist handbook. Durban: Jean Pujol Natural Healers Foundation; 1990.
42. Sewram V, Raynor MW, Mulholland DA, Raidoo DM. The uterotonic activity of compounds isolated from the supercritical fluid extract of *Ekebergia capensis*. J Pharm Biomed Anal 2000;24:133-45.
43. Jiofack T, Fokunang C, Guedje N, Kemeuze V, Fongnzossie FE, Nkongmeneck BA, *et al*. Ethnobotanical uses of medicinal plants of two ethno ecological regions of Cameroon. Int J Med Med Sci 2010;2:60-79.
44. Lulekal E, Asfaw Z, Kelbessa E, Van Damme P. Ethnomedicinal study of plants used for human ailments in Ankober District, North Shewa zone, Amhara Region, Ethiopia. J Ethnobiol Ethnomed 2013;9:63.
45. Mabogo DE. The Ethnobotany of the Vhavenda [M.S. thesis]: Pretoria: University of Pretoria; 1990.
46. Girmay T, Teshome Z. Assessment of traditional medicinal plants used to treat human and livestock ailments and their threatening factors in Gulomekeda District, Northern Ethiopia. Int J Emerg Trends Sci Technol 2017;4:5061-70.
47. Kama-Kama F, Midiwo J, Nganga J, Maina N, Schiek E, Omosa LK, *et al*. Selected ethno-medicinal plants from Kenya with *in vitro* activity against major African livestock pathogens belonging to the *Mycoplasma mycoides* cluster. J Ethnopharmacol 2016;192:524-34.
48. Amusan OO, Sukati NA, Dlamini PS, Sibandze FG. Some Swazi phytomedicines and their constituents. Afr J Biotechnol 2007;6:267-72.
49. York T, de Wet H, van Vuuren SF. Plants used for treating respiratory infections in rural Maputaland, KwaZulu-Natal, South Africa. J Ethnopharmacol 2011;135:696-710.
50. Zerabruk S, Yirga G. Traditional knowledge of medicinal plants in Gindeberet District, Western Ethiopia. S Afr J Bot 2012;78:165-9.
51. Rabe T, Van Staden J. Antibacterial activity of South African plants used for medicinal purposes. J Ethnopharmacol 1997;56:81-7.
52. Grierson DS, Afolayan AJ. An ethnobotanical study of plants used for the treatment of wounds in the Eastern Cape, South Africa. J Ethnopharmacol 1999;67:327-32.
53. Getaneh S, Girma Z. An ethnobotanical study of medicinal plants in debre libanos wereda, central Ethiopia. Afr J Plant Sci 2014;8:366-79.
54. Jeruto P, Too E, Mwamburi LA, Amuka O. An inventory of medicinal plants used to treat gynaecological obstetric-urino-genital disorders in South Nandi sub county in Kenya. J Nat Sci Res 2015;5:136-52.
55. Eguale T, Tilahun G, Gidey M, Mekonnen Y. *In vitro* anthelmintic activities of four Ethiopian medicinal plants against *Haemonchus contortus*. Pharmacol Online 2006;3:153-65.
56. Ndukwe IG, Habila JD, Bello IA, Adeleye EO. Phytochemical analysis and antimicrobial screening of crude extracts from the leaves, stem bark and root bark of *Ekebergia senegalensis* A. Juss. Afr J Biotechnol 2006;5:1792-4.
57. Amoo SO, Aremu AO, Moyo M, Van Staden J. Antioxidant and acetyl cholinesterase-inhibitory properties of long-term stored medicinal plants. BMC Complem Altern Med 2012;12:87.
58. Murata T, Miyase T, Muregi FW, Naoshima-Ishibashi Y, Umehara K, Warashina T, *et al*. Antiplasmodial triterpenoids from *Ekebergia capensis*. J Nat Prod 2008;71:167-74.
59. Irungu BN, Orwa JA, Gruhnojic A, Fitzpatrick PA, Landberg G, Kimani F, *et al*. Constituents of the roots and leaves of *Ekebergia capensis* and their potential antiplasmodial and cytotoxic activities. Molecules 2014;19:14235-46.
60. Bagla VP, McGaw LJ, Eloff JN. The antiviral activity of six South African plants traditionally used against infections in ethno veterinary medicine. Vet Microbiol 2012;155:198-206.
61. Mulholland DA, Lourine SE. Limonoids from *Ekebergia capensis*. Phytochem 1998;47:1357-61.
62. Lontsi D, Ayafor JF, Sondengam BL, Connolly JD, Rycroft DS. The use of two-dimensional long-range δ_C/δ_H correlation in conjunction with the one-dimensional proton-coupled ^{13}C NMR spectrum in the structural elucidation of ekeberginine, a new carbazole alkaloid from *Ekebergiasenegalensis* (Meliaceae). Tetrahedron Lett 1985;26:4249-52.
63. Okogun JI, Enyenihi VU, Ekong DE. Spectral studies on coumarins and the determination of the constitution of ekersenin by total synthesis. Tetrahedron 1978;34:1221-4.
64. Taylor DA. Ekebergin, a limonoid extractive from *Ekebergia capensis*. Phytochem 1981;20:2263-5.
65. Mulholland DA, Mahomed HA, Lourine S. A comparison of extractives from the bark of *Ekebergia capensis* and *Ekebergia senegalensis*. S Afr J Bot 1997;63:259-60.
66. Nishiyama Y, Moriyasu M, Ichimaru M, Tichibana Y, Kato A, Mathenge SG, *et al*. Acyclic triterpenoids from *Ekebergia capensis*. Phytochem 1996;42:803-7.
67. Vambe M, Aremu AO, Chukwujekwu JC, Finnie JF, Van Staden J. Antibacterial screening, synergy studies and phenolic content of seven South African medicinal plants against drug-sensitive and-resistant microbial strains. S Afr J Bot 2018;114:250-9.
68. Sofidiya MD, Odukoya OA, Familoni OB, Inya-Agha SI. Free radical scavenging activity of some Nigerian medicinal plant extracts. Pak J Biol Sci 2006;9:1438-41.
69. Jäger AK, Hutchings A, Van Staden J. Screening of Zulu medicinal plants for prostaglandin-synthesis inhibitors. J Ethnopharmacol 1996;52:95-100.
70. William A, Ngulde SI, Tijjani MB, Malgwi BU, Sandabe UK. Analgesic activities of the aqueous extract of *Ekebergia senegalensis* A. Jussstem bark in albino rats. Continental J Pharmacol Toxicol Res 2013;6:17-21.
71. McGaw LJ, Jäger AK, Van Staden J. Antibacterial, anthelmintic and anti-amoebic activity in South African medicinal plants. J Ethnopharmacol 2000;72:247-63.
72. York T, Van Vuuren SF, de Wet H. An antimicrobial evaluation of plants used for the treatment of respiratory infections in rural Maputaland, KwaZulu-Natal, South Africa. J Ethnopharmacol 2012;144:118-27.
73. Mabona U, Viljoen A, Shikanga E, Marston A, van Vuuren S. Antimicrobial activity of Southern African medicinal plants with dermatological relevance: From an ethnopharmacological screening approach, to combination studies and the isolation of a bioactive compound. J Ethnopharmacol 2013;148:45-55.
74. Lall N, Meyer JJ. *In vitro* inhibition of drug-resistant and drug-sensitive strains of *Mycobacterium tuberculosis* by ethnobotanically selected South African plants. J Ethnopharmacol 1999;66:347-54.
75. Kamadyaapa DR, Gondwe MM, Moodley K, Ojewole JA, Musabayane CT. Cardiovascular effects of *Ekebergia capensis* Sparrm (*Meliaceae*) ethanolic leaf extract in experimental animal paradigms. Cardiovasc J Afr 2009;20:162-7.
76. Tagne RS, Telefo BP, Nyemb JN, Yemele DM, Njima SN, Goka SM, *et al*. Anticancer and antioxidant activities of methanol extracts and fractions of some Cameroonian medicinal plants. Asian Pac J Trop Med 2014;7:s442-7.
77. Clarkson C, Maharaj VJ, Crouch NR, Grace OM, Pillay P, Matsabisa MG, *et al*. *In vitro* antiplasmodial activity of medicinal plants native to or naturalised in South Africa. J Ethnopharmacol 2004;92:177-91.
78. Muregi FW, Ishih A, Miyase T, Suzuki T, Kino H, Amano T, *et al*. Antimalarial activity of methanolic extracts from plants used in Kenyan ethnomedicine and their interactions with chloroquine (CQ) against a CQ-tolerant rodent parasite, in mice. J Ethnopharmacol 2007;111:190-5.
79. Chukwuma OC. *Meliaceae* plants and vector control of malaria: Larvicidal studies of *Ekebergia senegalensis* A Juss and *Cedrela odorata* Linn. Planta Med 2013;79:sl45.
80. Musili R, Muregi F, Mwatha J, Muriu D, M'rewa L, Kamau T, *et al*. Antischistosomal Activity of *Azadirachta indica* and *Ekebergia capensis* in Mice Infected with *Schistosoma mansoni*. Eur J Med Plant

2015;6:92-102.

81. Mokoka TA, Xolani PK, Zimmermann S, Hata Y, Adams M, Kaiser M, *et al*. Antiprotozoal screening of 60 South African plants, and the identification of the antitry panosomal germacranolides schkuhrin I and II. Planta Med 2013;79:1380-4.
82. Elgorashi EE, Taylor JL, Maes A, Van Staden J, De Kimpe N, Verschaeve L. Screening of medicinal plants used in South African traditional medicine for genotoxic effects. Toxicol Lett 2003;143:195-207.
83. Taylor JL, Elgorashi EE, Maes A, Gorp UV, De Kimpe N, Van Staden J, *et al*. Investigating the safety of plants used in South African traditional medicine: Testing for genotoxicity in the micronucleus and alkaline comet assays. Environ Mol Mutagenesis 2003;42:144-54.
84. Reid KA, Maes J, Maes A, Van Staden J, De Kimpe N, Mulholland DA, *et al*. Evaluation of the mutagenic and antimutagenic effects of South African plants. J Ethnopharmacol 2006;106:44-50.
85. Maroyi A. *Dicoma anomala* Sond: A review of its botany, ethnomedicine, phytochemistry and pharmacology. Asian J Pharm Clin Res 2018;11:70-7.
86. Ansari I, Patil DT. A brief review on phytochemical and pharmacological profile of *Carissa spinarum* L. Asian J Pharm Clin Res 2018;11:12-8.