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

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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, antihelmintic, antibacterial, anti-fungal, antinococcal, antimycobacterial, antinocplasmal, antihyperpertensive, antioxidant, antimalarial and antiplasmodial, antiischistosomal, antirypanosomal, 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.

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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 tetraterpenoids 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 Karl Gustaf Ekeberg (1716–1794), 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 pterophyla (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, Afrotamone and riverine forests on well drained and deep
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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, galloyl tannins, 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 antiparasitic activities exhibited by compounds 8, 24 [58], 23, 41, and 42 [59]. *In vivo* antimalarial activities exhibited by compound 24 [58], cytotoxic activities...
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exhibited by compounds 23, 24, 26, and 43 [60], and toxicity activities demonstrated by compounds 9 and 10 [61].

### 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 | [23,3,38] |
| Gastrointestinal problems (diarrhea, dysentery, gastritis, and stomach ache) | Bark, fruits, leaves, roots, and stem bark | Ethiopia, Kenya, South Africa, Swaziland, and Uganda | [1,21,24-26,37,38-40] |
| **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 | [1,12,17,24-26,32,36,45,46] |
| 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 | [1,12,18,23,25,26,39,40,47-50] |
| 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]       |
| Vener al 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                | Bark maceration taken orally mixed with those of Diospyros lycioides Desf. | South Africa | [17] |
| Blood in feces                                | Bark mixed with roots of Euclea natalensis A. DC. | South Africa | [18] |

### 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], antifungal [25,56,72,73], antihypertensive [19,75], antioxidant [27,57,68,76], antimalarial and antimalarial [33,34,58,77-79], antischistosomal [80], 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 inhibitor

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 |
|-----|----------|----------------------------|------------------|------------|
| 1   | Ekeberginine | NMR | Stem bark | [62] |
| 2   | Ekersin | NMR | Stem bark | [58,63] |
| 3   | 4,6-dimethoxy-5-methylcoumarin | NMR | Stem bark | [58] |
| 4   | 7-hydroxy-6-methoxycoumarin | NMR | Wood | [42] |
| 5   | Xanthonyletin | NMR | Stem bark | [62] |
| 6   | Kaempferol-3-O-β-D-glucopyranoside | MS and NMR | Leaves | [59] |
| 7   | Quercetin-3-O-β-D-glucopyranoside | MS and NMR | Leaves | [59] |
| 8   | 7-deacetoxy-7-oxygenunin | NMR | Stem bark | [58] |
| 9   | Capensolactones 1 | MS and NMR | Seeds | [61] |
| 10  | Capensolactones 2 | MS and NMR | Seeds | [61] |
| 11  | Capensolactones 3 | MS and NMR | Seeds | [61] |
| 12  | Ekeberginin | 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] |
| 17  | Atraric acid | NMR | Bark | [65] |
| 18  | β-sitosterol | NMR | Bark and wood | [42,65] |
| 19  | β-sitosterol oleate | NMR | Bark | [65] |
| 20  | β-sitosterol palmitate | NMR | Bark | [65] |
| 21  | (2Z)-volkendousin | NMR | Stem bark | [58] |
| 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-olean-28,13β-olide | MS and NMR | Root bark and stem bark | [58,59] |
| 27  | 7-acetylenestrilchilenone | 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 (% leucocyanidin 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 (µg 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 2.14 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 doses 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 ethanol extracts of *E. capensis* in an in vitro assay for cyclooxygenase (COX) inhibitors with indomethacin (0.5 mg/L) as the control. The ethanolic extract of *E. capensis* 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 (IC₅₀) values. Water bark extracts showed half maximal IC₅₀ 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 [41,51,52], pain and swelling of jaws in Ethiopia [52,46], 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]. Egalue 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 0.25 mg/ml to induce 100% egg hatching inhibition while the hydroalcoholic extracts did not induce complete inhibition at the highest concentration tested of 2 mg/ml. The aqueous extract induced 50% inhibition (ED₅₀) at 0.06 mg/ml while the ED₅₀ value of hydroalcoholic extract was 1.03 mg/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 8 mg/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 [1,12,23,47].

**Antibacterial**

Rabe and VanStaden [51] evaluated antibacterial activities of water and methanol bark extracts of *E. capensis* against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *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. epidermidis*, 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*, *P. aeruginosa*, *S. aureus*, and *S. epidermidis* 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 dichloromethane-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 >16.0 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], diarrhoea 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].

**Antagonococcal**

Mulaudzi et al. [25] evaluated the antagonococcal 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 negative and positive 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, Yameh et al. [67] evaluated the antagonococcal 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 antagonococcal activities exhibited by *E. capensis* extracts tested in this study could lead to the isolation of lead antagonococcal compounds.

**Antimycobacterial**

Lal 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]. Mulaudi 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 B 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] assayed antifungal properties of aqueous and dichloromethanol (1:1) leaf extract of the fourth instar larvae 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 dichloromethane-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 dichloromethane-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 weaning 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 weaning 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 vasorelaxation 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 (IC₅₀) value of 1.33 µg/mL which was comparable to IC₅₀ value of 1.42 µg/mL exhibited by rutin, a pure standard antioxidant compound [28]. 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 IC₅₀ values of 4.7 µg/mL to 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 IC₅₀ value of 15.8 µg/mL and 29.9 µg/mL, which was comparable to IC₅₀ values of 22.7 µg/mL and 108.3 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 IC₅₀ value of 36.66 µg/mL and ethyl acetate, butanol and methanol were active with IC₅₀ values ranging from 26.1 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 IC₅₀ values of 10 µg/mL and 18 µg/mL respectively [77]. Muregi et al. [53] evaluated antiplasmodial activities of chloroform, ethyl acetate, and hexane and methanol leaf extracts of *E. capensis* using the [G₄H₄] 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 IC₅₀ 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 IC₅₀ values of 6 µM and 7 µM, respectively [58]. Iru dug 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 IC₅₀ values ranging from 18.2 µM to 20.7 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 IC₅₀ 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 chloroquine 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 and stem bark 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 NN-diethyl-3-methylbenzamide as a reference.
insecticide. The hexane fraction displayed mortality at 0.63 mg/mL with LC50 value of 0.81 mg/mL which was comparable to the LC50 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 [36], 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 [61] evaluated antitrypanosomal activities of dichloromethane-methanol root extracts of E. capensis against Trypanosoma brucei rhodesiense using serial dilution. The extract exhibited activity with LC50 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 myoblast L-6 cells with an IC50 value of 33.0 µg/mL [81].

Antiviral
Baga 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 EC50 values ranging from 30.9 µg/mL to 78.2 µg/mL with selectivity index values of <1 [60]. Muluzdi 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 µg/mL based on COX assay, with bark and leaf water extracts exhibiting dose-dependent IC50 values of 0.01±0.00 mg/mL while leaf methanol extract exhibited IC50 value 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 (IC50) values ranging from 13.5 µg/mL to 28.8 µg/mL which were comparable to IC50 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 IC50 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 cytotoxic and/or aneugenic activity although micronuclear frequencies were well below that found for the positive control mitomycin in 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 mouse micronutagenicity 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 [ED50] of 0.14 µg/mL). The extract lacked toxicity to KB cells with ED50 value >2.0 µg/mL and selectivity index value >5.1. Bagga 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 (IC50) values ranging from 2.5 µg/mL to 45.1 µg/mL with selectivity index values of<1. Mulaudzi et al [26] evaluated genotoxicity activities of dichloromethane, ethanone, 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 against 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; therefore, the extract could be classified as a weak mutagen [26]. Irunu 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 42 isolated 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 IC50 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 IC50 values of 1.4 µM and 13.3 µM against the HEp2 and 4T1 cells, respectively [59].

Uterotonic
Sevaram 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. Sevaram 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
Mulohlland 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, pythoesters, pregnane, saponins, tannins, and withaenoids 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, antihelmintic, antibacterial, antifungal, antioxidant, and antiplasmodial, anti proliferative, antichistolom, antirypansomal, and 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.

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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.

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