Review

Medicinal Uses, Phytochemistry and Pharmacological Properties of *Elaeodendron transvaalense*

Alfred Maroyi 1,* and Sebua Silas Semenya 2

1 Medicinal Plants and Economic Development (MPED) Research Centre, Department of Botany, University of Fort Hare, Private Bag X1314, Alice 5700, South Africa

2 Technology Transfer Office, Research Administration and Development Department, University of Limpopo, Private Bag X1106, Sovenga 0727, South Africa; sebusemenya@gmail.com

* Correspondence: amaroyi@ufh.ac.za; Tel.: +27-7196-00326

Received: 3 February 2019; Accepted: 27 February 2019; Published: 4 March 2019

Abstract: *Elaeodendron transvaalense* is a plant species, which is in high demand as a herbal medicine in southern Africa. This study critically reviewed the medicinal applications, phytochemistry, and pharmacological activities of *E. transvaalense*. The literature on medicinal applications, phytochemical, and pharmacological activities of *E. transvaalense*, was collected from multiple internet sources including Elsevier, Google Scholar, SciFinder, Web of Science, Pubmed, BMC, Science Direct, and Scopus. Complementary information was gathered from pre-electronic sources, such as books, book chapters, theses, scientific reports, and journal articles obtained from the University library. This study revealed that the species is used as herbal medicine in 62.5% of the countries where *E. transvaalense* is native in southern Africa. It is mainly used as herbal medicine for diarrhoea, menorrhagia, stomach aches, skin infections, inflammations, and rashes. Phytochemical compounds identified from the species, include flavonoids, peltogynoid, phenols, proanthocyanidins, tannin, and triterpenes. Ethnopharmacological research revealed that extracts and phytochemical constituents isolated from *E. transvaalense* have antibacterial, antifungal, anti-HIV, anti-inflammatory, antioxidant, antiplasmodial, anti-protozoan, anti-pyretic, hypoglycaemic, larvicidal, cytotoxicity, and mutagenic activities. *Elaeodendron transvaalense* should be subjected to detailed phytochemical, pharmacological, and toxicological evaluations aimed at correlating the medicinal uses of the species with the ethnopharmacological properties of the species.

Keywords: Celastraceae; *Elaeodendron transvaalense*; herbal medicine; southern Africa

1. Introduction

*Elaeodendron transvaalense* (Burtt Davy) R. H. Archer is a shrub or small to medium-sized tree belonging to the Celastraceae family. The species is commonly known as anthill saffron or bushveld saffron. The synonyms of *E. transvaalense* include *Cassine transvaalensis* (Burtt Davy) Codd, *Crocoxylon transvaalense* (Burtt Davy) N. Robson, *E. croceum* (Thunb.) DC. var. *heterophyllum* Loes., *Pseudocassine transvaalensis* (Burtt Davy) Bredell and *Salacia transvaalensis* Burtt Davy [1,2]. The species has been recorded in deciduous woodland, along streams, rocky hillsides, and termite mounds in Botswana, Angola, Namibia, Mozambique, Zimbabwe, South Africa, Zambia, and Swaziland [1,2]. *Elaeodendron transvaalense* is popular as a traditional medicine in southern Africa and in South Africa, Raimondo et al. [3] categorized the species as Near Threatened using the IUCN Red List of Categories and Criteria of threatened species. There is a steady decline in the wild population of *E. transvaalense* in South Africa, which is attributed to over-harvesting, destructive harvesting of the bark, marketing of the plant products, and land clearing for agricultural and urbanization purposes. *Elaeodendron transvaalensis* was identified by both rural and urban herbalists as one of 15 species...
that are becoming increasingly rare in the KwaZulu-Natal province in South Africa [4], and was ranked twelfth among the most frequently demanded medicinal species in the same province [5]. Elaeodendron transvaalense is sold in informal herbal medicine markets in five of the nine provinces (55.6%) in South Africa, that is, the Eastern Cape, KwaZulu Natal, Gauteng, Limpopo, and the Western Cape [4–14]. Research by Williams et al. [7] showed that E. transvaalense was available in 48% to 70% of herbal medicine informal markets in Johannesburg, Gauteng province, and about 11,155 kg to 27,771 kg of the species’ bark were traded per annum as a herbal medicine in 2001 in Gauteng province alone [15]. Due to the increasing demand for the species, E. transvaalense is managed in herbal medicine home gardens in the Limpopo and North West provinces in South Africa [16,17]. This study reviewed the medicinal applications, phytochemical, and pharmacological activities of E. transvaalense, based on its therapeutic potential as a herbal medicine in southern Africa. Therefore, the aim of this review was to provide a detailed appraisal of the existing knowledge and literature on the medicinal uses, phytochemistry, biological activities, and pharmacological properties of E. transvaalense, in an attempt to create a database of information that can be used in future research aimed at exploring the therapeutic potential of the species.

2. Medicinal Uses of Elaeodendron transvaalense

Medicinal uses of the species have been recorded in Botswana, Swaziland, Namibia, Zimbabwe, and South Africa, accounting for 62.5% of the countries where E. transvaalense is native. The bark and root macerate of E. transvaalense are used as herbal medicines against several diseases in southern Africa, see Table 1. Elaeodendron transvaalense is used as herbal concoction for diarrhoea in South Africa and Swaziland [10,18–23], menorrhagia in Botswana, South Africa, and Zimbabwe [20,24,25], stomach aches in South Africa and Swaziland [19–23,26–29], skin infections, inflammations and rashes in Namibia, South Africa, and Swaziland [19,20,30–32]. The roots or root bark of E. transvaalense are mixed with the roots of Peltophorum africanum Sond. As a herbal medicine for female infertility [33] or mixed with roots of Ozoroa paniculosa (Sond.) R. Fern. & A. Fern. as a herbal medicine for high blood pressure [25]. The roots of E. transvaalense are mixed with Drimia elata Jacq. bulb, roots of Elephantorrhiza elephantina (Burch.) Skeels and Zanthoxylum capense (Thunb.) Harv., bark of Sclerocarya birrea (A. Rich.) Hochst. and Sarcostemma viminale (L.) R. Br. twigs as herbal medicines for human immunodeficiency virus (HIV) opportunistic infections [34] and sexually transmitted infections (STIs) [35]. Bark and leaves of E. transvaalense are used as an ethnoveterinary medicine for diarrhoea and worms [36,37].

Table 1. Medicinal uses of Elaeodendron transvaalense.

| Medicinal Use          | Parts of the Plant Used                  | Country          | References |
|------------------------|-----------------------------------------|------------------|------------|
| Abdominal pains        | Bark and roots                          | Zimbabwe         | [24]       |
| Anthelmintic           | Root bark                               | South Africa     | [22,38]    |
| Arthritis              | Root bark                               | Botswana         | [39]       |
| Backache               | Root bark                               | Botswana         | [25,39]    |
| Bladder infections     | Bark                                    | South Africa     | [22]       |
| Blood cleanser         | Roots                                   | South Africa     | [29]       |
| Body pains             | Bark                                    | South Africa     | [20]       |
| Candidiasis            | Roots                                   | South Africa     | [40]       |
| Chest pains            | Roots mixed with bulb of Drimia elata Jacq. | South Africa   | [41]       |
| Cough                  | Bark                                    | South Africa     | [22]       |
| Diabetes               | Bark                                    | South Africa     | [21]       |
| Diarrhoea              | Bark                                    | South Africa and Swaziland | [10,18–23] |
| Emetic                 | Stem                                    | Swaziland        | [19,27]    |
| Female infertility     | Bark or roots mixed with Peltophorum africanum Sond. bark and decoction taken orally | South Africa     | [33]       |
Table 1. Cont.

| Medicinal Use               | Parts of the Plant Used | Country                  | References                      |
|-----------------------------|-------------------------|--------------------------|---------------------------------|
| Fever                       | Bark                    | South Africa             | [10,20,21,23,26,29]             |
| Haemorrhoids                | Root bark               | South Africa             | [22,36]                         |
| High blood pressure         | Root bark mixed with roots of *Ozoroa paniculosa* (Sond.) R. Fern. & A. Fern. | Botswana | [42] |
| High blood pressure         | Roots                   | Botswana                 | [43]                            |
| HIV/AIDS                    | Roots mixed with *Drinia elata* Jacq. bulb, roots of *Elephantorrhiza elephantina* (Burch.) Skeels and *Zanthoxylum capense* (Thunb.) Harv., bark of *Sclerocarya birrea* (A. Rich.) Hochst. and *Sarcostemma viminale* (L.) R. Br. twigs | South Africa | [34] |
| Induce vomiting             | Stem bark               | South Africa             | [46,47]                         |
| Intestinal cramps           | Bark                    | South Africa             | [10,15,20,21]                   |
| Kidney infections           | Bark                    | South Africa             | [22]                            |
| Laxative                    | Bark                    | South Africa             | [22]                            |
| Malaria                     | Bark                    | South Africa             | [48]                            |
| Menorrhagia                 | Root bark mixed with roots of *Ozoroa paniculosa* | Botswana | [42] |
| Menstrual problems          | Roots and stem bark     | South Africa             | [16,45,46,50]                   |
| Sexually transmitted infections (STIs) | Roots mixed with *Drinia elata* bulb, roots of *Elephantorrhiza elephantina* and *Zanthoxylum capense*, bark of *Sclerocarya birrea* and *Sarcostemma viminale* twigs | South Africa | [35] |
| Skin infections, inflammations and rashes | Bark | Namibia, South Africa and Swaziland | [19,20,30–32] |
| Sore throat                 | Leaves                  | South Africa             | [32]                            |
| Stomach aches               | Bark and roots          | Swaziland and South Africa | [19–23,26–29]                  |
| Stomach cleanser            | Bark                    | South Africa             | [10]                            |
| Venereal diseases           | Root bark               | South Africa             | [22,36]                         |
| Wounds                      | Bark                    | Namibia                  | [51]                            |

Ethnoveterinary Medicine

| Medicines                  |                        |                          |                                 |
|---------------------------|-------------------------|--------------------------|---------------------------------|
| Diarrhoea                  | Bark and leaves         | South Africa             | [36,37]                         |
| Worms                      | Leaves                  | South Africa             | [37]                            |

3. Phytochemical Constituents of *Elaeodendron transvaalense*

A wide range of minerals and phytochemicals (Table 2) have been isolated from the stem bark, leaves and the bark of *E. transvaalense*. Phytochemical screening of ethanol, hexane, and hexane: Ethyl acetate (80: 20) extracts of root and stem bark yielded carbohydrate, flavonoid, peltogynoid and triterpenes (Table 3; Figure 1). Drewes et al. [52] isolated canophyllal, (+)-11,11-dimethyl-1,3,8,10-trahydroxy-9-methoxy-peltogynan, 6β-hydroxy-lup-20(30)-en-3-one, canophyllol and galactitol from the roots of *E. transvaalense*. Mothanka et al. [39] isolated a flavonoid 4′-O-methyl-epigallocatechin from the aqueous root extract of *E. transvaalense*. Tshikalange and Hussein [53] isolated triterpenes lup-20(29)-ene-30-hydroxy-3-one, β-sitosterol, Ψ-taraxastanol and lup-20(30)-ene-3α,29-diol and a flavonoid 4′-O-methyl-epigallocatechin from *E. transvaalense* bark ethanol extract. Mthethwa et al. [23] isolated triterpenoids, 3,28-dihydroxy-lup-20(29)-ene and 3-oxo-28-hydroxy-lup-20(29)-ene from the hexane: ethyl acetate (80: 20) bark extracts of *E. transvaalense*. Mamba et al. [46] isolated triterpenoids lup-20(30)-ene-3α,29-diol and lup-20(29)-ene-30-hydroxy-3-one, as well as a flavonoid 4′-O-methyl-epigallocatechin from
E. transvaalense bark ethanol extract. Khumalo et al. [54] isolated triterpenes 30-hydroxylup-20(29)-ene-3-one, lup-20(30)-ene-3α,29-diol and 6β-hydroxy-lup-20(29)-ene-3-one and a flavonoid 4′-O-methyl-epigallocatechin from aqueous and dichloromethane stem bark extracts of E. transvaalense.

Table 2. Mineral and phytochemical composition of Elaeodendron transvaalense.

| Mineral and Phytochemical Composition | Values          | Plant Parts   | References |
|--------------------------------------|-----------------|---------------|------------|
| Al (mg/kg dry weight (dw))           | 26.5–41.6       | Stem bark     | [55]       |
| As (mg/kg dw)                       | 0.06            | Stem bark     | [55]       |
| Cr (mg/kg dw)                       | 4.8             | Stem bark     | [55]       |
| Cu (mg/kg dw)                       | 2.8–3.5         | Stem bark     | [55]       |
| Fe (mg/kg dw)                       | 59.0–206.0      | Stem bark     | [55]       |
| Flavonoid (mg catechin equivalents/g dw) | 0.1–0.2        | Stem bark     | [48,55]    |
| Hg (mg/kg dw)                       | 2.4–8.2         | Stem bark     | [55]       |
| Mn (mg/kg dw)                       | 11.3–12.7       | Stem bark     | [55]       |
| Ni (mg/kg dw)                       | 1.8–2.6         | Stem bark     | [55]       |
| Pb (mg/kg dw)                       | 1.2             | Stem bark     | [55]       |
| Proanthocyanidin (mg/g)             | 0.25            | Bark          | [48]       |
| Sn (mg/kg dw)                       | 40.2–42.1       | Stem bark     | [55]       |
| Sulphur hydryl (µg/g)               | 0.36            | Bark          | [48]       |
| Tannin (mg/mL gallic acid equivalent)| 0.4–0.8        | Leaves        | [56]       |
| Total phenolics (mg of gallic acid equivalent/g of extract) | 0.04–9.4 | Bark and leaves | [48,55,57] |
| Zn (mg/kg dw)                       | 3.8–4.4         | Stem bark     | [55]       |

Figure 1. Cont.
4. Pharmacological Activities

4.1. Antibacterial Activities

McGaw et al. [58] evaluated the antibacterial activities of aqueous, ethanol, and hexane bark extracts of *E. transvaalense* against *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumoniae*, and...

Figure 1. Chemical structures of compounds isolated from *Elaeodendron transvaalense*. 
Table 3. Phytochemical composition of *Elaeodendron transvaalense*.

| Phytochemical Compound | Extract/Plant Part | References |
|------------------------|--------------------|------------|
| **Carbohydrate**       |                    |            |
| Galactitol             | Ethanol Root bark  | [52]       |
| **Flavonoid**          |                    |            |
| 4’-O-methyl-epigallocatechin | Dichloromethane, ethanol and water Stem bark | [39,53,54] |
| **Peltogynoid**        |                    |            |
| (+)-11,11-dimethyl-1,3,8,10-tetrahydroxy-9-methoxypeltogynan | Ethanol Root bark | [52] |
| **Triterpenes**        |                    |            |
| 3-oxo-28-hydroxybetuli-20(29)-ene | Hexane: ethyl acetate Bark | [23] |
| 3,28-dihydroxybetuli-20(29)-ene | Hexane: ethyl acetate Bark | [23] |
| 30-hydroxylup-20(29)-ene-3-one | Dichloromethane and water Root bark | [54] |
| 6β-hydroxy-lup-20(29)-ene-3-one | Dichloromethane and water Root bark | [54] |
| Canophyllal            | Ethanol and hexane | Root bark  | [52] |
| Canophyllol            | Ethanol and hexane | Root bark  | [52] |
| Lup-20(30)-ene-3α,29-diol | Dichloromethane, ethanol and water Stem bark | [46,53,54] |
| Lup-20(29)-ene-30-hydroxy-3-one | Ethanol Stem bark | [46,53] |
| β-sitosterol           | Ethanol Stem bark  | [53]       |
| Ψ-taraxastananol       | Ethanol Stem bark  | [53]       |

4. Pharmacological Activities

4.1. Antibacterial Activities

McGaw et al. [58] evaluated the antibacterial activities of aqueous, ethanol, and hexane bark extracts of *E. transvaalense* against *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* using the disc-diffusion and micro-dilution assays, with neomycin (5 µg) as the positive control (Table 4). Ethanol and water extracts were active with minimum inhibitory concentration (MIC) values ranging from 0.1 mg/mL to 0.8 mg/mL against *Bacillus subtilis* and *Staphylococcus aureus* [58]. Samie et al. [59] evaluated the antibacterial activities of methanol root extracts of *E. transvaalense* against *Aeromonas hydrophila*, *Bacillus cereus*, *Bacillus pumilus*, *Bacillus subtilis*, *Enterobacter cloacae*, *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pasteurella agglomerans*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Salmonella cholerae-suis*, *Serratia marcescens*, *Shigella flexneri*, and *Staphylococcus aureus* using the disc diffusion and the microdilution methods with gentamicin as a positive control. The extracts showed activities against most of the tested microbes with the exception of *Klebsiella pneumoniae*, *Serratia marcescens*, and *Shigella flexneri* with the zone of inhibition ranging from 8 mm to 10 mm (Table 4). The extracts showed activities against *Aeromonas hydrophila*, *Bacillus pumilus*, *Bacillus subtilis* *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Salmonella cholerae-suis*, *Serratia marcescens*, and *Staphylococcus aureus*, with MIC values ranging from 6 mg/mL to >12 mg/mL [59]. Tshikalanga et al. [60] evaluated the antibacterial activities of aqueous and chloroform bark extracts of *E. transvaalense* against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Serratia marcescens*, and *Staphylococcus aureus* using the agar dilution method. The extracts were active against *Bacillus cereus*, *Bacillus pumilus*, *Bacillus subtilis*, and *Staphylococcus aureus* with MIC values ranging from 20 mg/mL to 50 mg/mL [60]. Steenkamp et al. [31] evaluated the antibacterial activities of methanol and water bark extracts of *E. transvaalense* against *Escherichia coli*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Pseudomonas aeruginosa* using the plate-hole diffusion and broth microdilution methods with ampicillin as the positive control. The extracts were active against *Staphylococcus aureus* and *Staphylococcus epidermidis* exhibiting MIC values ranging from 1.3 mg/mL to 17.2 mg/mL and the positive control exhibited MIC value of 0.2 mg/mL [31]. Mthethwa et al. [23] evaluated antibacterial activities of *E. transvaalense* bark extracts against *Staphylococcus aureus* and *Staphylococcus epidermidis* using Kirby-Bauer disk diffusion and micro-dilution techniques.
with cloxacillin and dimethyl sulfoxide (DMSO) as positive, and negative controls, respectively. The extracts exhibited activities with zones of inhibition ranging from 23 mm to 31 mm (Table 4). The MIC values ranged from 0.6 µg/mL to 0.02 µg/mL [23]. Okem et al. [55] evaluated the antibacterial activities of ethanol stem bark extracts of *E. transvaalense* against *Escherichia coli* and *Staphylococcus aureus*, using the microdilution assay with neomycin as the positive control. The extracts exhibited activities with MIC values ranging from 0.8 mg/mL to 3.1 mg/mL [55]. Mamba et al. [46] evaluated the antibacterial activities of ethanol bark extracts of *E. transvaalense* and the compounds lup-20(30)-ene-3α,29-diol, lup-20(29)-ene-30-hydroxy-3-one and 4′-O-methyl-epigallocatechin isolated from the species against *Gardnerella vaginalis*, *Neisseria gonorrhoeae*, and *Oligella ureolytica* using the serial broth microdilution assay with ciprofloxacin as a positive control. The extracts and compounds exhibited activities with MIC values ranging from 1.6 mg/mL to 12.5 mg/mL, while the control exhibited MIC value of 0.01 mg/mL [46]. Khumalo et al. [54] evaluated antibacterial activities of dichloromethane and methanol stem bark extracts of *E. transvaalense* and compounds lup-20(30)-ene-3α,29-diol, 6β-hydroxy-lup-20(29)-ene-3-one, 30-hydroxy-lup-20(29)-ene-3-one and 4′-O-methylepigallocatechin isolated from the species against *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Shigella sonnei*, *Staphylococcus aureus*, and *Staphylococcus epidermidis* using the micro-titre plate broth two-fold serial dilution assay with ciprofloxacin as the positive control. The extract and the compounds demonstrated moderate antibacterial activities with MIC values ranging from 0.1 mg/mL to 1.7 mg/mL [54]. These findings corroborate the traditional use of the species as a herbal medicine for diarrhoea [10,18–23], sexually transmitted infections [16,35,45,46,50], skin infections [19,20,30–32], sore throat [32], stomach aches [19–23,26–29], venereal diseases [22,38], and wounds [51].

| Activity Tested | Extract | Plant Part | Model | Effect | Reference |
|-----------------|---------|------------|-------|--------|-----------|
| Antibacterial   | Methanol| Bark       | Kirby-bauer disk diffusion | Exhibited activities with zone of inhibition of 23 mm and 25 mm to 31 mm against *Staphylococcus aureus* and *Staphylococcus epidermis*, respectively | [23] |
| Antibacterial   | Methanol| Bark       | Micro-dilution technique | Minimum inhibitory concentration (MIC) values varied between 0.6 µg/mL and 0.02 µg/mL and extracts inhibited 6% of *Staphylococcus aureus* and 2% *Staphylococcus epidermidis* at a minimum concentration of 0.02 µg/mL | [23] |
| Antibacterial   | Aqueous | Bark       | Plate-hole diffusion and broth microdilution methods | Extracts exhibited activities with MIC values of 17.2 mg/mL against both *Staphylococcus epidermidis* and *Staphylococcus aureus* | [31] |
| Antibacterial   | Methanol| Bark       | Plate-hole diffusion and broth microdilution methods | Extracts exhibited activities with MIC values of 1.3 mg/mL and 2.5 mg/mL against *Staphylococcus epidermidis* and *Staphylococcus aureus*, respectively | [31] |
| Antibacterial   | Ethanol | Bark       | Serial broth microdilution | Extracts exhibited activities with MIC values of 12.5 mg/mL, 1.6 mg/mL and 3.1 mg/mL against *Gardnerella vaginalis*, *Neisseria gonorrhoeae* and *Oligella ureolytica* | [46] |
| Antibacterial   | Dichloromethan | Bark | Micro-titre plate broth two-fold serial dilution assay | Extracts exhibited activities with MIC values of 0.4 mg/mL against *Pseudomonas aeruginosa*, 0.5 mg/mL against *Staphylococcus aureus* and *Staphylococcus epidermidis*, *Escherichia coli* (0.7 mg/mL), *Shigella sonnei* (0.8 mg/mL) and *Salmonella typhimurium* (1.0 mg/mL) | [54] |
| Antibacterial   | Methanol | Bark       | Micro-titre plate broth two-fold serial dilution assay | Extracts exhibited activities with MIC value of 1.3 mg/mL against *Escherichia coli*, *Staphylococcus aureus* and *Salmonella typhimurium*, 1.0 mg/mL against *Pseudomonas aeruginosa* and *Shigella sonnei*, and *Staphylococcus epidermidis* (1.7 mg/mL) | [54] |
| Activity Tested | Extract | Plant Part | Model | Effect | Reference |
|----------------|---------|------------|-------|--------|-----------|
| Antibacterial  | Ethanol | Stem bark  | Microdilution assay | Extracts exhibited activities with MIC values of 3.1 mg/mL and 0.78 to 1.6 mg/mL against *Escherichia coli* and *Staphylococcus aureus*, respectively | [55] |
| Antibacterial  | Aqueous | Bark       | Microdilution assay | Extracts exhibited activities with MIC values of 0.8 mg/mL and 0.2 mg/mL against *Bacillus subtilis* and *Staphylococcus aureus*, respectively | [58] |
| Antibacterial  | Ethanol | Bark       | Microdilution assay | Extracts exhibited activities with MIC values of 0.2 mg/mL and 0.1 mg/mL against *Bacillus subtilis* and *Staphylococcus aureus*, respectively | [58] |
| Antibacterial  | Aqueous | Bark       | Disc-diffusion assays | Extracts exhibited activities with MIC values of 0.2 mg/mL and 0.3 mg/mL against *Bacillus subtilis* and *Staphylococcus aureus*, respectively | [58] |
| Antibacterial  | Ethanol | Bark       | Disc-diffusion assays | Extracts exhibited activities with MIC values of 0.2 mg/mL and 0.6 mg/mL against *Bacillus subtilis* and *Staphylococcus aureus*, respectively | [58] |
| Antibacterial  | Methanol | Roots     | Disc diffusion method | Exhibited activities with zone of inhibition of 23 mm against *Bacillus cereus*, 8 mm against *Bacillus pumilus*, *Staphylococcus aureus*, *Enterococcus clatiae*, *Escherichia coli*, *Aeromonas hydrophila*, *Proteus mirabilis* and *Salmonella cholera-suis* and 10 mm against *Bacillus subtilis*, *Enterococcus faecalis*, *Pantoea agglomerans* and *Pseudomonas aeruginosa* | [59] |
| Antibacterial  | Methanol | Roots     | Microdilution method | Exhibited activities with MIC values of 12 mg/mL against *Bacillus pumilus*, *Bacillus subtilis*, *Enterococcus clatiae* and *Escherichia coli*, 6 mg/mL against *Klebsiella pneumoniae*, *Staphylococcus aureus* and *Salmonella cholera-suis* >12 mg/mL against *Aeromonas hydrophila*, *Proteus mirabilis* and *Serratia marcescens* | [59] |
| Antibacterial  | Aqueous | Bark       | Agar diffusion method | Extracts exhibited activities with MIC values of 50.0 mg/mL against *Bacillus cereus* and *Bacillus pumilus*, 20.0 mg/mL against *Bacillus subtilis* and *Staphylococcus aureus* | [60] |
| Antifungal     | Methanol | Bark       | Plate-hole diffusion and broth microdilution methods | Extract exhibited activities with MIC value of 20.2 mg/mL | [61] |
| Antifungal     | Hexane  | Bark       | Agar diffusion assay | Exhibited activities with zone of inhibition of 12 mm to 16 mm against *Candida albicans*, *Candida krusei* (8 mm to 14 mm) and *Cryptococcus neoformans* (14 mm to 16 mm) | [22] |
| Antifungal     | Hexane  | Bark       | Microdilution assay | Exhibited activities with MIC values of 0.5 mg/mL against *Candida albicans* and 1.9 mg/mL against both *Candida krusei* and *Cryptococcus neoformans* | [22] |
| Antifungal     | Hexane  | Bark       | Microdilution assay | Exhibited activities with minimum fungicidal concentration (MFC) values of 3.8 mg/mL against *Candida albicans*, *Candida krusei* (7.5 mg/mL) and *Cryptococcus neoformans* (1.9 mg/mL) | [22] |
| Antifungal     | Hexane  | Bark       | Time-to-kill experiments | Extract was able to kill >90% of all cells of *Candida albicans* at a concentration of 1.9 mg/mL after a 10 hour incubation | [22] |
| Antifungal     | Ethanol | Bark       | Serial broth microdilution | Extracts exhibited activities with MIC values of 3.1 mg/mL against *Candida albicans* | [46] |
| Anti-HIV       | Aqueous | Root       | RNA-dependent-DNA polymerase (RDDP) activity of HIV-1 reverse transcriptase | Extracts exhibited activities with half maximal inhibitory concentration (IC₅₀) value of 80.0 µg/mL | [44] |
### Table 4. Cont.

| Activity Tested | Extract     | Plant Part | Model                                                                 | Effect                                                                 | Reference |
|-----------------|-------------|------------|----------------------------------------------------------------------|----------------------------------------------------------------------|-----------|
| Anti-HIV        | Methanol    | Root       | RNA-dependent-DNA polymerase (RDDP) activity of HIV-1 reverse transcriptase | Extracts exhibited activities with IC$_{50}$ value of 131.0 µg/mL      | [44]      |
| Anti-HIV        | Aqueous     | Root       | RNase H assay                                                          | Extracts exhibited activities with IC$_{50}$ value of 31.2 µg/mL      | [44]      |
| Anti-HIV        | Methanol    | Root       | RNase H assay                                                          | Extracts exhibited activities with IC$_{50}$ value of 30.0 µg/mL      | [44]      |
| Anti-HIV        | 70% acetone | Stem bark  | NF-kB assay                                                            | Extracts showed inhibitory activities of 45% to 54%                   | [50]      |
| Anti-HIV        | Chloroform  | Stem bark  | NF-kB assay                                                            | Extracts showed inhibitory activities of 57% to 73%                   | [50]      |
| Anti-HIV        | Ethyl acetate | Stem bark  | NF-kB assay                                                            | Extracts showed inhibitory activities of 72% to 76%                   | [50]      |
| Anti-HIV        | 70% acetone | Stem bark  | HeLa-Tat-Luc assay                                                     | Extracts showed inhibitory activities of 22% to 43%                   | [50]      |
| Anti-HIV        | Chloroform  | Stem bark  | HeLa-Tat-Luc assay                                                     | Extracts showed inhibitory activities of 28% to 76%                   | [50]      |
| Anti-HIV        | Chloroform  | Stem bark  | HeLa-Tat-Luc assay                                                     | Extracts showed inhibitory activities of 63% to 75%                   | [50]      |
| Anti-HIV        | Methanol    | Bark       | Anti-HIV-1$_{lab}$ assay                                               | Exhibited activities with half maximal effective concentration (EC$_{50}$) value of 0.1 µg/mL and 0.2 µg/mL | [62]      |
| Anti-HIV        | Methanol    | Bark       | Anti-HIV-1$_{lab}$ assay                                               | Exhibited activities with EC$_{50}$ value of 3.5 µg/mL                | [23]      |
| Anti-HIV        | Ethanol     | Bark       | HIV-RT colorimetric assay                                              | Extract exhibited inhibitory activity of 20%                          | [46]      |
| Anti-HIV        | Aqueous     | Bark       | Reverse transcriptase (RT) assay                                       | Extract showed inhibition ranging from 25% to 40%                     | [63]      |
| Anti-inflammatory | Aqueous  | Root bark  | Cyclooxygenase (COX) inhibition assay                                  | Extract exhibited 90% PGE$_2$ inhibition in lipopolysaccharide (LPS) induced RAW 264.7 macrophages | [64]      |
| Anti-inflammatory | Ethanol  | Bark       | Lipoyxgenase (15-LOX) inhibitory assay                                 | Extract exhibited activities with IC$_{50}$ value of 80.2 µg/mL       | [46]      |
| Antioxidant     | Aqueous     | Roots      | 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging assay    | Above 200 µg/mL, the extract showed 80% scavenging activity           | [65]      |
| Antioxidant     | Ethanol     | Roots      | DPPH free radical scavenging assay                                     | Above 100 µg/mL, the extract showed 80% scavenging activity          | [65]      |
| Antioxidant     | Aqueous     | Roots      | DPPH free radical scavenging assay                                     | Above 200 µg/mL, the extract showed 80% scavenging activity          | [39]      |
| Antioxidant     | Ethanol     | Roots      | DPPH free radical scavenging assay                                     | Above 100 µg/mL, the extract showed 80% scavenging activity          | [39]      |
| Antioxidant     | Methanol    | Bark       | Hydroxyl (•OH) radical scavenging assay                                | Exhibited activities with IC$_{50}$ values of 3.6 mg/mL               | [48]      |
| Antioxidant     | Methanol    | Bark       | Super oxide (SO) assay                                                 | Exhibited activities with IC$_{50}$ values of 1.6 mg/mL               | [48]      |
| Antioxidant     | Methanol    | Bark       | Nitric oxide (NO) radical scavenging assay                             | Exhibited activities with IC$_{50}$ values of 3.6 mg/mL               | [48]      |
| Antioxidant     | Methanol    | Bark       | Iron chelating property assay                                          | Exhibited activities with IC$_{50}$ values of 3.9 mg/mL               | [48]      |
| Antioxidant     | Methanol    | Bark       | DPPH free radical scavenging assay                                     | Exhibited activities with IC$_{50}$ values of 0.7 mg/mL               | [48]      |
| Antioxidant     | Methanol    | Bark       | 2,2’-azinobis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS) radical scavenging assays | Exhibited activities with IC$_{50}$ values of 4.1 mg/mL               | [48]      |
Table 4. Cont.

| Activity Tested | Extract | Plant Part | Model | Effect | Reference |
|-----------------|---------|------------|-------|--------|-----------|
| Antioxidant     | Methanol| Leaves     | DPPH  | Exhibited activities with IC\textsubscript{50} value of 2.8 mg/mL. | [57] |
| Antiplasmodial  | Dichloromethane| Bark | Plasmodium falciparum | Plasmodium falciparum lactate dehydrogenase assay | Extract exhibited activities with IC\textsubscript{50} value of 5.1 µg/mL. | [48] |
| Anti-protozoan   | Aqueous  | Bark       | Serial two-fold dilution | Extract exhibited activities with MIC value of 9.7 mg/mL against *Trichomonas vaginalis* | [66] |
| Anti-pyretic     | Methanol | Bark       | In vivo experiments using female and male Sprague-Dawley rats | Extracts exhibited potential to reduce pyrexia in the induced rats and activities were time and concentration dependent with extracts showing activity as early as from 30 minutes and even at the lowest concentration of 100 mg/kg | [48] |
| Hypoglycaemic   | Acetone  | Stem bark  | In vitro anti-diabetic and toxicity screening against murine C2C12 myoblasts, Chang liver cells and 3T3-L1 preadipocytes | Extracts had potential of 138.6% to lower blood glucose levels at a concentration of 50 µg/mL against 3T3-L1 preadipocytes and 100% against both C2C12 myoblasts and Chang liver cells. | [67] |
| Hypoglycaemic   | Acetone  | Stem bark  | α-amylase inhibiting activity | Extract exhibited activity with IC\textsubscript{50} value of 1.1 µg/mL. | [67] |
| Hypoglycaemic   | Acetone  | Stem bark  | α-glucosidase inhibiting activity | Extract exhibited activity with IC\textsubscript{50} value of 50.6 µg/mL. | [67] |
| Larvicidal      | Dichloromethane| Bark | Larvicidal assay on *Culex quinquefasciatus* larvae | Extracts exhibited activities with 60% mortality and IC\textsubscript{50} value of 18.2 µg/mL. | [48] |
| Larvicidal      | Methanol | Bark       | Larvicidal assay on *Culex quinquefasciatus* larvae | Extracts exhibited activities with 47% mortality and IC\textsubscript{50} value of 9.8 µg/mL. | [48] |
| Cytotoxicity    | Ethanol  | Stem bark  | 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) calorimetric assay | Extracts exhibited activities at 12.5 µg/mL showing 90% and 40% of viable 3T3-L1 preadipocytes and Chang liver cells, respectively of the control | [67] |
| Cytotoxicity    | Ethanol  | Stem bark  | XTT (sodium 3’-[1-(phenylamino-carbonyl)-3,4-tetrazolium]-bis-[4-methoxy-6-nitro] benzene sulfonic acid hydrate) colorimetric assay | Extracts exhibited activities with IC\textsubscript{50} values >100.0 µg/mL in both Vero cells and MCF-7 cell line | [53] |
| Cytotoxicity    | Methanol | Stem bark  | 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay | Extracts exhibited activities with half maximal cytotoxic concentration (CC\textsubscript{50}) value of 3.7 µg/mL. | [62] |
| Cytotoxicity    | Dichloromethane| Bark | MTT cell proliferation assay | Extracts exhibited activities with the median lethal concentration (LC\textsubscript{50}) value of 512.0 µg/mL and 394.0 µg/mL against human embryonic kidney (HEK293) and human hepatocellular carcinoma (HepG2) cells, respectively | [48] |
| Cytotoxicity    | Methanol | Bark       | 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) calorimetric assay | Extracts exhibited activities with CC\textsubscript{50} value of 200.0 µg/mL and selective index (SI) value of 57.1 | [23] |
Table 4. Cont.

| Activity Tested | Extract  | Plant Part | Model                        | Effect                                                                 | Reference |
|-----------------|----------|------------|------------------------------|----------------------------------------------------------------------|----------|
| Cytotoxicity    | Aqueous  | Bark       | MTT cell proliferation assay | Extracts exhibited activities in all the three human tumour cancer cell lines | [63]     |
| Cytotoxicity    | 70% acetone | Stem bark | Cytotoxicity assay on MT2 cells | Extracts showed cell death of 22.7% after 36 h at the highest concentration tested of 15 µg/mL | [50]     |
| Cytotoxicity    | Chloroform | Stem bark | Cytotoxicity assay on MT2 cells | Extracts showed cell death of 27.6% after 36 h at the highest concentration tested of 15 µg/mL | [50]     |
| Cytotoxicity    | Ethyl acetate | Stem bark | Cytotoxicity assay on MT2 cells | Extracts showed cell death of 17.1% after 36 h at the highest concentration tested of 15 µg/mL | [50]     |
| Antimutagenicity | Methanol | Leaves     | Ames test                    | Extract exhibited weak antimutagenic activities with 23.2% inhibition of 4-nitroquinoline 1-oxide in Salmonella typhimurium TA98 and 21.3% in strain TA100 at the assayed concentration of 5 mg/mL | [57]     |

4.2. Anti-Fungal Activities

Steenkamp et al. [61] evaluated the anti-fungal activities of methanol and the water bark extracts of *E. transvaalense* against *Candida albicans* standard strain (ATCC 10231), and five clinical isolates using the plate-hole diffusion and broth microdilution methods, with amphotericin B as the positive control (Table 4). Only the methanol extract was active against the standard strain (ATCC 10231) exhibiting an MIC value of 20.2 mg/mL, while the positive control amphotericin B inhibited growth of all strains tested with an MIC value of <10 µg/mL [61]. Samie et al. [22] evaluated the anti-fungal activities of acetone and hexane bark extracts of *E. transvaalense* against *Candida albicans*, *Candida krusei*, and *Cryptococcus neoformans* using the agar diffusion and the microdilution methods, with nystatin and flucytosine as positive controls. Only hexane extract exhibited activities with the zone of inhibition ranging from 8 mm to 16 mm in comparison to 22 mm exhibited by both nystatin and flucytosine, the two positive controls. The MIC values against tested pathogens ranged from 0.5 mg/mL to 1.9 mg/mL, while the positive controls, nystatin and flucytosine, exhibited MIC values of 0.2 µg/mL, and 1.9 µg/mL, respectively. The minimum fungicidal concentration (MFC) values ranged from 1.9 mg/mL to 7.5 mg/mL (Table 4). The time-to-kill experiments indicated an intense time-dependent fungicidal effect of the hexane extract against *Candida albicans*, able to kill >90% of all the cells at a concentration of 1.9 mg/mL after a 10 hour incubation [22]. Mamba et al. [46] evaluated the antifungal activities of ethanol bark extracts of *E. transvaalense* and the compounds lup-20(30)-ene-3α,29-diol, lup-20(29)-ene-30-hydroxy-3-one and 4’-O-methyl-epigallocatechin, isolated from the species against *Candida albicans*, using the serial broth microdilution assay. The extracts and compounds exhibited activities with MIC values ranging from 3.1 mg/mL to <12.5 mg/mL [46]. These documented antifungal activities corroborate the use of the species as herbal medicine against candidiasis in South Africa [40], skin infections, and rashes [19,20,30–32].

4.3. Anti-HIV Activities

Morobe et al. [62] evaluated the anti-HIV activities of methanolic bark extracts of *E. transvaalense*, using the anti-HIV-1<sub>1/2</sub> assay (Table 4). The extract exhibited the ability to inhibit HIV-1<sub>1/2</sub> with half maximal effective concentration (EC<sub>50</sub>) values of 0.1 µg/mL and 0.2 µg/mL [62]. Bessong et al. [44] evaluated the anti-HIV activities of aqueous and methanol root extracts of *E. transvaalense* by assessing their inhibitory properties against HIV-1 reverse transcriptase (RT). The strongest inhibition was against the ribonuclease H (RNase H) activity of RT with methanol and aqueous extracts exhibiting half maximal inhibitory concentration (IC<sub>50</sub>) values of 30.0 µg/mL, and 31.2 µg/mL, respectively, while the inhibitory on RNA-dependent-DNA polymerase (RDDP) activity of RT for aqueous and methanol extracts exhibited IC<sub>50</sub> values of 80.0 µg/mL, and 131.0 µg/mL, respectively [44]. Tshikalange et
al. [50] evaluated the anti-HIV activities of 70% acetone, chloroform and ethyl acetate stem bark extracts of *E. transvaalense* by assessing their inhibition against α-glycohydrolase, reverse transcriptase, and viral proteins (NF-kB and Tat), which play a significant role in the HIV life cycle with mesuol as a positive control. In the in vitro assay of α-glycohydrolase, the extracts showed no inhibition against α-glycohydrolase, but the chloroform and ethyl acetate extracts showed good inhibitory activities of 64%, and 76%, respectively at the lowest concentration tested (1 µg/mL) in the NF-kB assay (Table 4). At the highest concentration 1 µg/mL, 70% acetone extract exhibited an inhibition of 54%, chloroform (73%) and ethyl acetate (75%), which was comparable to 84% exhibited by mesuol, the positive control. Chloroform and ethyl acetate extracts showed a high Tat inhibitory activity of 73%, and 75%, respectively at 15 µg/mL, while 70% acetone extract demonstrated a lower activity of 43%. The extracts showed lower cell death percentages, ranging from 17.1% to 27.6% after 36 h at the highest concentration tested (15 µg/mL) [50]. Mthethwa et al. [23] evaluated anti-HIV activities of *E. transvaalense* bark extracts using the anti-HIV-1iiiB assay. The extract exhibited the ability to inhibit HIV-1iiiB with half the maximal effective concentration (EC50) value of 3.5 µg/mL [23]. Mamba et al. [46] evaluated anti-HIV activities of ethanol bark extracts of *E. transvaalense* and the compounds lup-20(30)-ene-3α,29-diol, lup-20(29)-ene-30-hydroxy-3-one, and 4’-O-methyl-epigallocatechin isolated from the species against recombinant HIV-1 enzyme, using non-radioactive HIV-RT colorimetric assay with doxorubicin as a positive control. The ethanol extract exhibited low inhibitory activity of 20%, 4’-O-methyl-epigallocatechin showed moderate activity of 63.7%, while the positive control doxorubicin showed 96.5% inhibitory activity [46]. Sigidi et al. [63] evaluated the anti-HIV activities of aqueous bark extract of *E. transvaalense* using the reverse transcriptase (RT) assay. The extract showed inhibition ranging from 25% to 40% [63]. These documented anti-HIV activities corroborate the use of the species as herbal medicine against HIV opportunistic infections in South Africa [16,34,35,44].

### 4.4. Anti-Inflammatory Activities

Mthethaka and Habtemariam [64] evaluated the anti-inflammatory activities of aqueous crude root bark extract of *E. transvaalense*, using the cyclooxygenase (COX) inhibition assay, with indomethacin as a positive control (Table 4). The extract (125 mg/mL) exhibited 90% PGE2 inhibition in lipopolysaccharide (LPS) induced RAW 264.7 macrophages, which is comparable to 100% PGE2 inhibition exhibited by indomethacin, the control drug [64]. Mamba et al. [46] evaluated the anti-inflammatory activities of ethanol bark extracts of *E. transvaalense* and the compounds lup-20(30)-ene-3α,29-diol, lup-20(29)-ene-30-hydroxy-3-one, and 4’-O-methyl-epigallocatechin isolated from the species by assessing the inhibitory effects on the pro-inflammatory enzyme, 15-lipoxygenase (15-LOX), with quercetin as a positive control. The extracts and compounds exhibited activities with IC50 values, ranging from 31.4 µg/mL to 80.2 µg/mL, which was comparable to IC50 value of 48.9 µg/mL exhibited by quercetin, the control [46]. These findings support the traditional use of the species as herbal medicine for abdominal pains [24], body pains [20], skin inflammations [19,20,30–32], and wounds [51].

### 4.5. Antioxidant Activities

Mthethaka et al. [65] evaluated the antioxidant activities of water and ethanol root extracts of *E. transvaalensis* and a compound 4’-O-methyl-epigallocatechin, isolated from the species using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging assay with quercetin, rutin, and ascorbic acid as positive controls. Above 100 µg/mL, the ethanolic extract showed an 80% scavenging activity, which was similar to the activities exhibited by the control antioxidant compounds quercetin, rutin, and ascorbic acid, and the water extract reached a similar of activity (80%) at 200 µg/mL (Table 4). Between 25.0 µg/mL to 50 µg/mL, the compound 4’-O-methyl-epigallocatechin exhibited a 65% scavenging activity, which was greater than the activities exhibited by both water and ethanol extracts. But at concentrations above 50 µg/mL, the scavenging activity of the ethanol extract exceeded that of the compound 4’-O-methyl-epigallocatechin [65]. Mthethaka et al. [39] evaluated
the antioxidant activities of water and ethanol root extracts of *E. transvaalensis* and a compound 4′-O-methyl-epigallocatechin, isolated from the species, using the DPPH free radical scavenging assay with quercetin, rutin, and ascorbic acid as positive controls. Both the crude extract and the compound 4′-O-methyl-epigallocatechin showed activities, and at 100 µg/mL, the ethanolic extract showed 80% scavenging activity, which was similar to the activities exhibited by the control antioxidant compounds quercetin, rutin, and ascorbic acid; while the water extract reached a similar level at 100 µg/mL [39]. Nethengwe et al. [48] evaluated the antioxidant activities of methanolic bark extracts of *E. transvaalense*, using the DPPH free radical scavenging, 2,2′-azinobis-3-ethylbenzothiazoline-6-sulphonate (ABTS), hydroxyl (•OH) radical scavenging, super oxide (SO), nitric oxide (NO) radical scavenging, iron chelating property assays, total antioxidant capacity, and the sulphur hydryl (SH) content (Table 4). The IC₅₀ values for the DPPH assay was 0.7 µg/mL, ABTS (4.1 µg/mL), iron chelating (3.9 µg/mL), •OH (3.6 µg/mL), NO (3.6 µg/mL) and SO (1.6 µg/mL) [48]. Makhafolo et al. [57] evaluated the antioxidant activities of methanol leaf extracts of *E. transvaalense*, using the DPPH free radical scavenging assay with ascorbic acid as the positive control. The extract exhibited activities with EC₅₀ value of 2.8 µg/mL, which was comparable to EC₅₀ value of 2.3 µg/mL exhibited by ascorbic acid, the positive control [57]. The antioxidant activities exhibited by the crude extracts of *E. transvaalense* are probably due to flavonoids and phenolics, which have been isolated from the species [48,53,55,57].

4.6. Antiplasmodial Activities

Nethengwe et al. [48] evaluated the anti-plasmodial activities of aqueous, dichloromethane, and methanolic bark extracts of *E. transvaalense* against the chloroquine sensitive strain of *Plasmodium falciparum* (D10), using the parasite lactate dehydrogenase assay (Table 4). The other extracts were not active with the exception of dichloromethane, which exhibited IC₅₀ value of 5.1 µg/mL [48]. These findings support the general view that *E. transvaalense* is a potential source of antimalarial agents and to some extent corroborate the traditional use of the species as herbal medicine against fever [10,20,21,23,26,29] and malaria [48].

4.7. Anti-Protozoan Activities

Fernandes et al. [66] evaluated the anti-protozoan activities of aqueous bark extract of *E. transvaalense* against *Trichomonas vaginalis*, using serial two-fold dilutions, with metronidazole as a positive control (Table 4). The extract showed activities with MIC value of 9.7 mg/mL while metronidazole exhibited MIC value of 0.5 µg/mL [66]. These findings corroborate the traditional use of the species as herbal medicine for sexually transmitted infections [16,35,45,46,50], skin infections [19,20,30–32], and venereal diseases [22,38].

4.8. Anti-pyretic Activities

Nethengwe et al. [48] evaluated the anti-pyretic activities of dichloromethane and methanolic bark extracts of *E. transvaalense*, using both female and male Sprague-Dawley rats with paracetamol as the reference drug (Table 4). The extracts exhibited the potential to reduce pyrexia in the induced rats and the activities were time- and concentration-dependent, with the extracts showing activity as early as 30 minutes, even at the lowest concentration of 100 mg/kg. The methanol extract showed significant activity that was comparable to paracetamol, the reference drug [48]. These findings corroborate the use of *E. transvaalense* as herbal medicine against fever [10,20,21,23,26,29].

4.9. Hypoglycaemic Activities

Deutschländer et al. [67] evaluated the hypoglycaemic activities of acetone stem bark extracts of *E. transvaalense*, by assessing their inhibiting effects on carbohydrate-hydrolysing enzymes α-glucosidase and α-amylase. The acetone extracts were screened against C2C12 myocytes, 3T3-L1 preadipocytes and Chang liver cells by measuring their glucose uptake (Table 4). The in vitro assay in 3T3-L1 preadipocytes indicated that the extracts had potential of 138.6% to lower blood glucose levels.
at a concentration of 50 µg/mL. The α-glucosidase and α-amylase 50% inhibitory concentrations (IC$_{50}$) of the extracts was found to be 50.6 µg/mL, and 1.1 µg/mL, respectively [67]. These results somehow support the usage of *E. transvaalense* as a herbal medicine against diabetes [66].

### 4.10. Larvicidal Activities

Nethengwe et al. [48] evaluated larvicidal activities of aqueous, dichloromethane, and methanolic bark extracts of *E. transvaalense*, using the mosquito larvicidal assay by the use of *Culex quinquefasciatus* larvae. The results of the percentage mortality of the fourth instar larvae of *Culex quinquefasciatus* showed that the aqueous extracts had least larvicidal activity of 35%, methanol (47%) and dichloromethane (60%) (Table 4). The IC$_{50}$ values of methanol and dichloromethane extracts were 9.8 µg/mL and 18.2 µg/mL, respectively [48]. These findings corroborate the use of *E. transvaalense* as herbal medicine against malaria [48].

### 4.11. Cytotoxicity and Mutagenic Activities

Deutschländer et al. [67] evaluated the cytotoxic activities of stem bark extracts of *E. transvaalense*, by assessing its effects on preadipocytes and hepatocytes cell lines (Table 4). The extract exhibited cytotoxicity at 12.5 µg/mL to 3T3-L1 preadipocytes, and Chang liver cells [67]. Tshikalange and Hussein [53] evaluated the cytotoxicity activities of the crude ethanolic extract and compounds lup-20(30)-ene-3α,29-diol, lup-20(29)-ene-30-hydroxy-3-one, Ψ-taraxastanol, β-sitosterol, and 4′-O-methyl-epigallocatechin isolated from *E. transvaalense* bark extract, using the XTT (sodium 3′-[1-(phenyl amino-carbonyl)-3,4-tetrazolium]-bis-[4-methoxy-6-nitro] benzene sulfonic acid hydrate) colorimetric assay against Vero and MCF-7 breast cancer cell lines, with doxorubicin and zelaralenone as positive controls. The cell lines were inhibited by all the compounds at the highest concentration tested (200 µg/mL), with the exception of crude extract and Ψ-taraxastanol. The crude extract, Ψ-taraxastanol and 4′-O-methyl-epigallocatechin had little or no toxicity on Vero cells by exhibiting IC$_{50}$ values greater than 100 µg/mL, while the crude extract and Ψ-taraxastanol also exhibited IC$_{50}$ values greater than 100 µg/mL in MCF-7 cell line. The IC$_{50}$ values of other compounds in both Vero cells and MCF-7 cell line ranged from 19.4 µg/mL to 96.0 µg/mL [53]. Morobe et al. [62] evaluated the cytotoxic activities of methanolic and aqueous extracts of *E. transvaalense* against MAGI CCR5+ cells, using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay. The extracts exhibited activities with half maximal cytotoxic concentration (CC$_{50}$) value of 3.7 mg/mL [62]. Nethengwe et al. [48] evaluated the cytotoxic activities of aqueous, dichloromethane, and methanolic bark extracts of *E. transvaalense*, using the MTT cell proliferation assay against human embryonic kidney (HEK293) and human hepatocellular carcinoma (HepG2) cells. The other extracts were not active with the exception of dichloromethane, which exhibited the median lethal concentration (LC$_{50}$) value of 512.0 µg/mL and 394.0 µg/mL against HEK293, and HepG2, respectively [48]. Mthethwa et al. [23] evaluated the cytotoxic activities of *E. transvaalense* bark extracts, using the MTT assay with berberine as a positive control. The CC$_{50}$ value of the extract was 200.0 µg/mL, which was higher than 27 µg/mL exhibited by berberine, the control and a selective index (SI) value of 57.1 [23]. Sigidi et al. [63] evaluated the cytotoxicity activities of aqueous bark extract of *E. transvaalense* on U937, MeWo, and Vero cell lines, using the MTT cell proliferation assay. The extract exhibited activities in all the three human tumour cancer cell lines [63].

Makhafola et al. [57] evaluated mutagenicity activities of methanolic leaf extracts of *E. transvaalense*, using the Ames test on *Salmonella typhimurium* strains TA98 and TA100. The authors also evaluated the antimutagenicity of the plant extracts against 4-nitroquinoline 1-oxide (4-NQO) using the Ames test. The extract did not exhibit any mutagenic activities, but showed weak antimutagenic activities (Table 4). The percentage inhibition of 4-NQO was 23.2% in *Salmonella typhimurium* TA98 and 21.3% in strain TA100 at the assayed concentration of 5 mg/mL [57].
5. Conclusion

The present review summarizes the medicinal uses, phytochemistry, and pharmacological properties *E. transvaalense*. The diverse pharmacological activities of *E. transvaalense* are somehow directly or indirectly involved in a range of physiological processes, which offer protection against both free radicals and harmful pathogens. In the past 30 years, *E. transvaalense* has been the subject of phytochemical and pharmacological research, but there is not yet enough data correlating the medicinal uses of the species with its phytochemical and pharmacological properties. Detailed studies on the pharmacokinetics, in vivo, and clinical research involving compounds isolated from *E. transvaalense* and extracts of the species are required. Therefore, future research should focus on the molecular modes or mechanisms of action, pharmacokinetics, and physiological pathways for specific extracts of the species, including the identification of the bioactive compounds of the species and their associated pharmacological activities. These studies need to be complemented with experimental animal studies, randomized clinical trials, and target-organ toxicity studies. The bark of *E. transvaalense* is known to be poisonous and there is need to do detailed toxicological evaluations that strike a balance between the medicinal potential, and adverse and toxic effects on the species. There is very little information on the toxicological properties of *E. transvaalense*, whether it causes superficial discomfort when ingested as herbal medicine or serious poisoning. In the absence of such detailed toxicological evaluations, the intake of *E. transvaalense* as a herbal medicine should, therefore, be done with caution as the species has potential to cause long-term damage in patients. The wide usage of *E. transvaalense* as a herbal medicine in southern Africa has resulted in an increased collection of its bark from the wild. The species population is declining due to harvesting for the medicinal plant trade, and this calls for conservation strategies and mechanisms to ensure sustainable utilization of the species.

**Author Contributions:** A.M. wrote the main body of the review manuscript and S.S.S. reviewed and commented the manuscript.

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

**Conflicts of Interest:** The authors declare no conflict of interest.

**References**

1. Archer, R.H.; Van Wyk, A.E. A taxonomic revision of *Elaeodendron* Jacq. (Cassinoideae: Celastraceae) in Africa. *S. Afr. J. Bot.* 1998, 64, 93–109. [CrossRef]
2. Germishuizen, G.; Meyer, N.L.; Steenkamp, Y.; Keith, M. *A Checklist of South African Plants*; Southern African Botanical Diversity Network: Pretoria, South Africa, 2006.
3. Raimondo, D.; Von Staden, L.; Foden, W.; Victor, J.E.; Helme, N.A.; Turner, R.C.; Kamundi, D.A. *Red List of South African Plants*; Strelitzia 25; South African National Biodiversity Institute: Pretoria, South Africa, 2009.
4. Cunningham, A.B. *An Investigation of the Herbal Medicine Trade in KwaZulu Natal*; Institute of Natural Resources Report 29; University of KwaZulu-Natal: Pietermaritzburg, South Africa, 1988.
5. Mander, M. *Marketing of Medicinal Plants in South Africa: A Case Study in KwaZulu-Natal*; Food and Agriculture Organization of the United Nations: Rome, Italy, 1998.
6. Cunningham, A.B. *African Medicinal Plants: Setting Priorities at the Interface between Conservation and Primary Health Care*; People and Plants Working Paper 1; UNESCO: Paris, France, 1993.
7. Williams, V.L.; Balkwill, K.; Witkowski, E.T.F. Unraveling the commercial market for medicinal plants and plant products on the Witwatersrand, South Africa. *Econ. Bot.* 2000, 54, 310–337. [CrossRef]
8. Williams, V.L.; Balkwill, K.; Witkowski, E.T.F. A lexicon of plants traded in the Witwatersrand umuthi shops, South Africa. *Bothalia* 2001, 31, 71–98. [CrossRef]
9. Tshisikhawe, M.P. Trade of Indigenous Medicinal Plants in the Northern Province, Venda Region: Their Ethnobotanical Importance and Sustainable Use. Master’s Thesis, University of Venda for Science and Technology, Thohoyandou, South Africa, 2002.
10. Ndawonde, B.G.; Zobolo, A.M.; Dlamini, E.T.; Siebert, S.J. A survey of plants sold by traders at Zululand muthi markets, with a view to selecting popular plant species for propagation in communal gardens. *Afr. J. Range Forage Sci.* 2007, 24, 103–107. [CrossRef]

11. Loundou, P.-M. Medicinal Plant Trade and Opportunities for Sustainable Management in the Cape Peninsula, South Africa. Master’s Thesis, University of Stellenbosch, Cape Town, South Africa, 2008.

12. Moeng, T.E. An Investigation into the Trade of Medicinal Plants by Muthi Shops and Street Vendors in the Limpopo Province, South Africa. Master’s Thesis, University of Limpopo, Sovenga, South Africa, 2010.

13. Tshisikhawhe, M.P.; Van Rooyen, M.W.; Bhat, R.B. An evaluation of the extent and threat of bark harvesting of medicinal plant species in the Venda Region, Limpopo Province, South Africa. *Phyton Int. J. Exp. Bot.* 2012, 81, 89–100.

14. Tshisikhawhe, M.P.; Van Rooyen, M.W. Population biology of *Elaeodendron transvaalense* Jacq. in the presence of harvesting. *Phyton Int. J. Exp. Bot.* 2013, 82, 303–311.

15. Williams, V.L.; Witkowski, E.T.F.; Balkwill, K. Volume and financial value of species traded in the medicinal plant markets of Gauteng, South Africa. *Int. J. Sustain. Dev. World Ecol.* 2007, 14, 584–603. [CrossRef]

16. Semenya, S.S.; Potgieter, M.J. Medicinal plants cultivated in Bapedi traditional healers homegardens, Limpopo province, South Africa. *Afr. J. Tradit. Complement. Altern. Med.* 2016, 1, 126–132. [CrossRef]

17. Cornelius, S.F. Health Clinic Gardens in North-West Province, South Africa, as Complex Social-Ecological Systems. Master’s Thesis, North West University, Potchefstroom, South Africa, 2016.

18. Pujol, J. *Natur Africa: The Herbalist Handbook, African Flora, Medicinal Plants*; Jean Pujol Natural Healers Foundation: Durban, South Africa, 1990.

19. Long, C. *Swaziland’s Flora: siSwati Names and Uses*; Swaziland National Trust Commission: Mbambane, Swaziland, 2005; Available online: http://www.sntc.org.sz/index.asp (accessed on 1 February 2019).

20. Van Wyk, B.-E.; Gericke, N. *People’s Plants: A Guide to Useful Plants of Southern Africa*; Briza Publications: Pretoria, South Africa, 2007.

21. Deutschländer, M.S.; Lall, N.; Van de Venter, M. Plant species used in the treatment of diabetes by South African traditional healers: An inventory. *Pharm. Biol.* 2009, 47, 348–365. [CrossRef]

22. Samie, A.; Tambani, T.; Harshfield, E.; Green, E.; Ramalivhana, J.N.; Bessong, P.O. Antifungal activities of selected venda medicinal plants against *Candida albicans, Candida krusei* and *Cryptococcus neoformans* isolated from South African AIDS patients. *Afr. J. Biotechnol.* 2010, 9, 2965–2976.

23. Mthethwa, N.S.; Oyedeji, B.A.O.; Obi, L.C.; Aiyegoro, A. Anti-staphylococcal, anti-HIV and cytotoxicity studies of four South African medicinal plants and isolation of bioactive compounds from *Cassine transvaalensis* (Burtt. Davy) Codd. *BMC Complement. Altern. Med.* 2014, 14, 512. [CrossRef] [PubMed]

24. Gelfand, M.; Mavi, S.; Drummond, R.B.; Ndemera, B. The Traditional Medical Practitioners in Zimbabwe: His Principles of Practice and Pharmacopoeia; Mambo Press: Gweru, Zimbabwe, 1985.

25. Motlhanka, D.; Nthoiva, G.P. Ethnobotanical survey of medicinal plants of Tswapong north, in eastern Botswana: A case of plants from Mosweu and Seolwane villages. *Eur. J. Med. Plants* 2013, 3, 10–24. [CrossRef]

26. Gerstner, J. A preliminary checklist of Zulu names of plants. *Bantu Stud.* 1939, 13, 131–149. [CrossRef]

27. Amusan, O.O.G.; Sukati, N.A.; Dlamini, P.S.; Sibandze, F.G. Some Swazi phytomedicines and their constituents. *Afr. J. Biotecnol.* 2007, 6, 267–272.

28. Chauke, M.A.; Shai, L.J.; Mogale, M.A.; Tshisikhawhe, M.P.; Mokgotho, M.P. Medicinal plant use of villagers in the Mopani district, Limpopo province, South Africa. *Afr. J. Tradit. Complement. Altern. Med.* 2015, 12, 9–26. [CrossRef]

29. Maema, L.P.; Mahlo, S.M.; Potgieter, M.J. Ethnomedicinal uses of indigenous plant species in Mogalakwena municipality of Waterberg district, Limpopo province, South Africa. *Int. J. Tradit. Complement. Med.* 2016, 1, 28–44.

30. Von Koenen, E. *Medicinal, Poisonous and Edible Plants in Namibia*; Klaus Hess Publishers: Windhoek, Namibia, 2001.

31. Steenkamp, V.; Fernandes, A.C.; Van Rensburg, C.E.J. Antibacterial activity of Venda medicinal plants. *Fitoterapia* 2007, 78, 561–564. [CrossRef] [PubMed]

32. Van Wyk, B.-E.; Van Oudtshoorn, B.; Gericke, N. *Medicinal Plants of South Africa*; Briza Publications: Pretoria, South Africa, 2013.
33. Semenya, S.S.; Maroyi, A.; Potgieter, M.J.; Erasmus, L.J.C. Herbal medicines used by Bapedi traditional healers to treat reproductive ailments in the Limpopo province, South Africa. Afr. J. Tradit. Complement. Altern. Med. 2013, 10, 331–339. [CrossRef] [PubMed]

34. Semenya, S.S.; Potgieter, M.J.; Erasmus, L.J.C. Ethnobotanical survey of medicinal plants used by Bapedi traditional healers to manage HIV/AIDS in the Limpopo province, South Africa. J. Med. Plants Res. 2013, 7, 434–441.

35. Semenya, S.S.; Potgieter, M.J.; Erasmus, L.J.C. Bapedi phytomedicine and their use in the treatment of sexually transmitted infections in Limpopo province, South Africa. Afr. J. Pharm. Pharmacol. 2013, 7, 250–262. [CrossRef]

36. Van der Merwe, D.; Swan, G.E.; Botha, C.J. Use of ethnoveterinary medicinal plants in cattle by Setswana-speaking people in the Madikwe area of the North West Province of South Africa. J. S. Afr. Vet. Assoc. 2001, 72, 189–196. [CrossRef] [PubMed]

37. Kunene, N.; Wilson, R.A.C.; Myeni, N.P. The use of trees, shrubs and herbs in livestock production by communal farmers in northern KwaZulu-Natal, South Africa. Afr. J. Range Forage Sci. 2003, 20, 271–274. [CrossRef]

38. Mabogo, D.E.N. The Ethnobotany of the Vhavenda. Master’s Thesis, University of Pretoria, Pretoria, South Africa, 1990.

39. Motlhanka, D.M.T.; Habtemariam, S.; Houghton, P. Free radical scavenging activity of crude extracts and 4′-O-methylgallocatechin isolated from roots of Cassine Transvaalensis Burtt-Davy from Botswana. Afr. J. Biomed. Res. 2008, 11, 55–63. [CrossRef]

40. Masevhe, N.A.; McGaw, L.J.; Eloff, J.N. The traditional use of plants to manage candidiasis and related infections in Venda, South Africa. J. Ethnopharmacol. 2015, 168, 364–372. [CrossRef] [PubMed]

41. Semenya, S.S.; Maroyi, A. Ethnobotanical survey of plants used by Bapedi traditional healers to treat tuberculosis and its opportunistic infections in the Limpopo Province, South Africa. S. Afr. J. Bot. 2018, 87, 66–75. [CrossRef]

42. Motlhanka, D.M.; Makhabu, S.W. Medicinal and edible wild fruit plants of Botswana as emerging new crop opportunities. J. Med. Plants Res. 2011, 5, 1836–1842.

43. Danley, K. Letters of the Bush: A Case Study of Traditional Setswana Herbal Medicine. Master’s Thesis, Carleton College, Northfield, MN, USA, 2006.

44. Bessong, P.O.; Obi, C.L.; Andreola, M.L.; Rojas, L.B.; Pousegu, L.; Igumbor, E.; Meyer, J.J.M.; Quideau, S.; Litvak, S. Evaluation of selected South African medicinal plants for inhibitory properties against human immunodeficiency virus type 1 reverse transcriptase and integrase. J. Ethnopharmacol. 2005, 99, 83–91. [CrossRef] [PubMed]

45. Semenya, S.S.; Maroyi, A. Indigenous plant species used by Bapedi healers to treat sexually transmitted infections: Their distribution, harvesting, conservation and threats. S. Afr. J. Bot. 2013, 87, 66–75. [CrossRef]

46. Mamba, P.; Adebayo, S.A.; Tshikalange, T.E. Anti-microbial, anti-inflammatory and HIV-1 reverse transcriptase activity of selected South African plants used to treat sexually transmitted diseases. Int. J. Pharmacogn. Phytochem. Res. 2016, 8, 1870–1876.

47. Tshikalange, T.E.; Mophuting, B.C.; Mahore, J.; Winterboer, S.; Lall, N. An ethnobotanical study of medicinal plants used in villages under Jongilanga Tribal council, Mpumalanga, South Africa. Afr. J. Tradit. Complement. Altern. Med. 2016, 13, 83–89. [CrossRef] [PubMed]

48. Nethengwe, M.F.; Opoku, A.R.; Dludla, P.V.; Madida, K.T.; Shonhai, A.; Smith, P.; Singh, M. Larvicidal, antipyretic and antiplasmodial activity of some Zulu medicinal plants. J. Med. Plants Res. 2012, 6, 1255–1262. [CrossRef]

49. Van Wyk, P. Trees of the Kruger National Park; Purnell: Cape Town, South Africa, 1972.

50. Tshikalange, T.E.; Meyer, J.J.M.; Lall, N.; Muñoz, E.; Sancho, R.; Van De Venter, M.; Oosthuizen, V. In vitro anti-HIV-1 properties of ethnobotanically selected South African plants used in the treatment of sexually transmitted diseases. J. Ethnopharmacol. 2008, 119, 478–481. [CrossRef] [PubMed]

51. Kasanda, C.D.; Kapenda, H.M. School learners’ knowledge and views of traditional medicinal plant use in two regions in Namibia. In Indigenous Knowledge of Namibia; Chinsembu, K.C., Cheikhyoussef, A., Mumbengegwi, D.R., Kandawa-Schulz, M., Kasandra, C.D., Kazembe, L., Eds.; University of Namibia Press: Windhoek, Namibia, 2015; pp. 135–156.
52. Drewes, S.E.; Mashimbye, M.J.; Field, J.S.; Ramesar, N. 11,11-dimethyl-1,3,8,10-tetrahydroxy-9-methoxypeltogynan and three pentacyclic triterpenes from Cassine transvaalensis. Phytochemistry 1991, 30, 3490–3493. [CrossRef]

53. Tshikalange, T.E.; Hussein, A. Cytotoxicity activity of isolated compounds from Elaeodendron transvaalesense ethanol extract. J. Med. Plants Res. 2010, 4, 1695–1697.

54. Khumalo, G.P.; Sadgrove, N.J.; Van Vuuren, S.E.; Van Wyk, B.-E. Antimicrobial lupenol triterpenes and a polyphenol from Elaeodendron transvaalesense, a popular southern African medicinal bark. S. Afr. J. Bot. 2018.

55. Okem, A.; Southway, C.; Stirk, W.A.; Street, R.A.; Finnie, J.F.; Van Staden, J. Heavy metal contamination in South African medicinal plants: A cause for concern. S. Afr. J. Bot. 2014, 93, 125–130. [CrossRef]

56. Würger, M.; McGaw, L.J.; Eloff, J.N. Tannin content of leaf extracts of 53 trees used traditionally to treat diarrhoea is an important criterion in selecting species for further work. S. Afr. J. Bot. 2014, 90, 114–117. [CrossRef]

57. Makhabola, T.J.; Elgorashi, E.E.; McGaw, L.J.; Verschaeve, L.; Eloff, J.N. The correlation between antimutagenic activity and total phenolic content of extracts of 31 plant species with high antioxidant activity. BMC Complement. Altern. Med. 2016, 16, 490. [CrossRef] [PubMed]

58. McGaw, L.J.; Jäager, A.K.; van Staden, J. Antibacterial, anthelmintic and anti-amoebic activity in South African medicinal plants. J. Ethnopharmacol. 2000, 72, 247–263. [CrossRef]

59. Samie, A.; Obi, C.L.; Bessong, P.O.; Namrita, L. Activity profiles of fourteen selected medicinal plants from rural Venda communities in South Africa against fifteen clinical bacterial species. Afr. J. Biotechnol. 2005, 4, 1443–1451.

60. Tshikalange, T.E.; Meyer, J.J.M.; Hussein, A.A. Antimicrobial activity, toxicity and the isolation of a bioactive compound from plants used to treat sexually transmitted diseases. J. Ethnopharmacol. 2005, 96, 515–519. [CrossRef] [PubMed]

61. Steenkamp, V.; Fernandes, A.C.; Van Rensburg, C.E.J. Screening of Venda medicinal plants for antifungal activity against Candida albicans. S. Afr. J. Bot. 2007, 73, 256–258. [CrossRef]

62. Morobe, I.C.; Mthethwa, N.S.; Bisi-Johnson, M.A.; Vasaikar, S.D.; Obi, C.L.; Oyedje, A.O.; Kambizi, L.; Eloff, J.N.; Hattori, T. Cytotoxic effects and safety profiles of extracts of active medicinal plants from South Africa. J. Microbiol. Res. 2012, 2, 176–182.

63. Sigidi, M.T.; Traore, A.N.; Boukandou, M.M.; Tshisikhawe, M.P.; Ntuli, S.S.; Potgieter, N. Anti-HIV, pro-inflammatory and cytotoxicity properties of selected Venda plants. Indian J. Tradit. Knowl. 2017, 16, 545–552.

64. Motlhanka, D.M.T.; Habtermariam, S. Prostaglandin E2 (PGE2) inhibition by crude extracts of selected medicinal plants from Botswana. Niger. J. Nat. Prod. Med. 2007, 11, 32–33.

65. Motlhanka, D.M.T.; Miljkovic-Brake, A.; Houghton, P.J.; Habtermarium, S.; Hylands, P.J. Antioxidant activity of water and ethanol extracts from roots of Cassine transvaalensis Burtt-Davy from Botswana. Planta Med. 2006, 72, P_057. [CrossRef]

66. Fernandes, L.; Van Rensburg, C.E.J.; Hoosen, A.A.; Steenkamp, V. In vitro activity of medicinal plants of the Venda region, South Africa, against Trichomonas vaginalis. South. Afr. J. Epidemiol. Infect. 2008, 23, 26–28. [CrossRef]

67. Deutschländer, M.S.; Van de Venter, M.; Roux, S.; Louw, J.; Lall, N. Hypoglycaemic activity of four plant extracts traditionally used in South Africa for diabetes. J. Ethnopharmacol. 2009, 124, 619–624. [CrossRef] [PubMed]