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# The Genus *Diospyros*: A Review of Novel Insights into the Biological Activity and Species of Mozambican Flora

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**Abstract:** Species of the *Diospyros* L. genus (*Ebenaceae* family) have been largely used in traditional medicine for the treatment of several diseases, especially infectious ones. To date, active major compounds such as naphthoquinones, triterpenoids, and tannins have been isolated and pharmacologically validated from *Diospyros* species. The present study summarizes the information available in the literature on the species described in the Flora of Mozambique. To do so, scientific databases (e.g., PubMed, Scopus, Web of Science, and Google Scholar) were searched using various keywords and Boolean connectors to gather and summarize the information. Of the 31 native and naturalized species in the Flora of Mozambique, 17 are used in different regions of Africa and were described for their traditional uses. They were reported to treat more than 20 diseases, mostly infectious, in the gastrointestinal and oral cavity compartments. This work provides an overview of the therapeutical potential of *Diospyros* species and explores novel insights on the antimicrobial potential of extracts and/or isolated compounds of these Mozambican species.

**Keywords:** antimicrobial activity; anti-inflammatory activity; cytotoxicity; *Diospyros*; ethnomedicinal practice; herbal medicine; infectious diseases



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## 1. Introduction

The genus *Diospyros* L. (*Ebenaceae* family) contains species that have been recognized and used in traditional medicine (extended ethnomedical use) and have potential new health benefits supported by in vitro biological, in vivo pharmacological, and clinical tests [1–4]. Furthermore, within certain cultures or communities, various traditional systems have used all plant parts of this botanical genus (leaf, fruit, bark, twig, hardwood, and root) as herbal medicines [1,4].

Beyond their pharmacological value, *Diospyros* spp. have distinct and complementary important qualities, namely valuable wood, and edible fruits, which provide significant economic benefits and are recognized and utilized in various industrial and commercial sectors [1,4].

Generally, *Diospyros* spp. are tree shrubs or subshrubs with entire alternate leaves, solitary flowers, and fleshy fruits (berries) with usually two or more seeds. The characteristics of the leaves and flowers of these species are often used to identify fossil casts [5–7].

*Diospyros* species are predominantly distributed between the tropics, and the most notable diversity of this botanical genus occurs in Africa [5,6,8]. As confirmed in The Plant List [9], the WFO Plant List currently contains 1575 species related to the genus *Diospyros*, of which 734 have accepted scientific names [10]. Regarding the Mozambican flora, the genus is represented by 31 species (Table 1), corresponding to 18 accepted scientific name species, seven accepted subspecies (subsp.), three species that are considered synonyms, and three species that are not yet in the WFO plant list as of 12 February 2022 [10–12].

**Table 1.** Species of the genus *Diospyros* L. present in Mozambican Flora.

| First Discription Year | Scientific Name | Author | Common Name English/Local | MD [1] | | | | | | | | IUCN [2] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | N | Z | T | MS | GI | M | CD | Np | |
| 1980 | *D. anitae* | F.White | malawi star apple/- | | | | | | | | | LC |
| 1911 | *D. bussei* | Gürke | coral star-berry/- | | | | | | | | | NT |
| 1935 | *D. consolatae* | Chiov. | -/novolo | | | | | | | | | LC |
| 1963 | *D. dichrophylla* | (Gand.) De Winter | poison star-apple/- | | | | | | | | | LC |
| 1933 | *D. ferrea* | (Willd.) Bakh. | -/- | | | | | | | | | A |
| 1962 | *D. inhacaensis* | F.White | coastal jackal-berry/dodo | | | | | | | | | LC |
| 1988 | *D. kabuyeana* | F.White | -/- | | | | | | | | | LC |
| 1873 | *D. kirkii* | Hiern | large-leaved jackal-berry/ cula, fuma, jacualala, mucula, murriba, tendje | | | | | | | | | LC |
| 1980 | *D. mafiensis* | F.White | -/- | | | | | | | | | NT |
| 1844 | *D. mespiliformis* | Hochst. ex A.DC. | african ebony, jackal-berry/ muribariba, mucula, muquéué, murriparipa, mutona, mussuma | | | | | ▽ | | | | LC |
| 1956 | *D. quiloensis* | (Hiern) F.White | crocodile-bark jackal-berry/ midodo, murodo | | | | | | | | | LC |
| 1873 | *D. rotundifolia* | Hiern | dune star-apple/ impapa, mapiti, munhentze | | | | Δ | | | | | NE |
| 1861 | *D. senensis* | Klotzsch | spiny jackal-berry/ matamba, mudalima, tombatica | | | | | | | | | LC |
| 1861 | *D. squarrosa* | Klotzsch | rigid star-berry/cachenz'ere, mpomopo, senzasicana, sicana | | | | | | | | | LC |
| 1980 | *D. truncatifolia* | Caveney | square-leaved star apple/ impope, mpope | | | | | | | | | LC |
| 1873 | *D. verrucosa* | Hiern | warty star-apple/djacola, mkonhomo, nkalanongo, riparipa | | | | | | | | | LC |
| 1961 | *D. whyteana* | (Hiern) P.White | bladder-nut/- | | | | | | | | | LC |
| 1963 | *D. zombensis* | (B.L.Burtt) F.White | malawi star-apple/- | | | | | | | | | LC |
| 1891 | *D. abyssinica* subsp. *abyssinica* | (Hiern) F.White | giant diospyros/- | | | | | | | | | LC |
| 1988 | *D. abyssinica* subsp. *attenuata* * | (Hiern) F.White | giant diospyros/- | | | | | | | | | LC |
| 1980 | *D. abyssinica* subsp. *chapmaniorum* | (Hiern) F.White | giant diospyros/- | | | | | | | | | LC |
| 1837 | *D. loureiriana* subsp. *loureiriana* [a] | G.Don | dye star-apple, sand star-apple/chipongoti, nhandima | | | | | | | | | LC |
| 1805 | *D. lycioides* Desf. subsp. *sericea* | (Bernh.) De Winter | eastern blue-bush, red star-apple/ chitomatomana, m'dima | | | | | | | | | LC |

**Table 1.** *Cont.*

| First Discription Year | Scientific Name | Author | Common Name English/Local | MD [1] | | | | | | | | IUCN [2] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | N | Z | T | MS | GI | M | CD | Np | |
| 1968 | *D. natalensis* subsp. *natalensis* * | (Harv.) Brenan | acorn jackal-berry/- | | | | | | | | | A |
| 2009 | *D. natalensis* subsp. *nummularia* | (Harv.) Brenan Jordaan | acorn diospyros, acorn jackal-berry, granite jackal-berry **/- | | | | | | | | | A |
| [b] *D. usambarensis* subsp. *usambarensis /rufescens* | | F.White | -/aboba, kidanko, mpome, nhamudima, popa | | | | | | | | | LC |
| [c] *D. villosa* (L.) var. *villosa* | | De Winter | hairy star-apple/nhachibabane, nhaurratane, chicanela, chicumbela, chibabane | | | | | | | | | A |
| [c] *D. villosa* var. *parvifolia* | | (De Winter) De Winter | hairy star-apple/- | | | | | | | | | A |
| [d] *D. consolatae-rotundifolia intermediates* | | - | - | | | | | | | | | A |
| [d] *D. kirkii-mespiliformis intermediates* | | - | - | | | | | | | | | A |
| [d] *D.* sp. no. 1 sensu FZ | | - | - | | | | | | | | | A |

[1] Distribution in Mozambique (blue, MD) [10,11]; Common name local (green, MD) [12]: N—Niassa; Z—Zambezia; T—Tete; MS—Manica and Sofala; GI—Gaza–Inhambane; M—Maputo; CD—Cabo Delgado; Np—Nampula; * Not identified; ** Other names—small-leaved jackal berry, Tickey tree; ∇: Gaza; Δ: Sofala. [2] International Union for the Conservation of Nature: LC—least concern; NE—not evaluated; NT—near threatened [B2ab(iii)]; A—absent. WFO Plant List: [a] *D. loureiroana* G.Don subsp. *loureiriana*; [b] Synonym of *D. loureiroana* subsp. *rufescens* (Caveney) Verdc.; [c] Synonym of *D. villosa* (L.) De Winter; [d] not included in the WFO Plant List [10,11]; (-)—not available.

Concerning primary health care (PHC), herbal medicines are used by 80% of the African population, and more than 70% of the population of Mozambique uses such medicines for treating all diseases [13–15]. For instance, several *Diospyros* species with antimicrobial potential have been reported [4,16–18]. Worldwide, the magnitude of infectious diseases (ID), encompassing antimicrobial resistance (AMR), represents a major health problem (approximately 700,000 people die every year) [19,20]. Infectious diseases have a high impact in Africa, particularly in Mozambique [21].

Most of the native and naturalized *Diospyros* species of Mozambique's flora are generally recognized as traditionally used in different regions of Africa to treat different diseases, with a particular focus on infections affecting the gastrointestinal tract and oral cavity. This work will present a comprehensive overview of the therapeutic potential of Mozambican *Diospyros* species based on chemical, biological, and toxicological experimental data, particularly addressing its antimicrobial properties and including comparative elements concerning the biological activity of other *Diospyros* species.

## 2. Results

### *2.1. Ethnomedical Use of Diospyros Species of Mozambican Flora*

Table 2 shows the results of the collected ethnomedical data from seventeen Mozambican species, namely *D. abyssinica*, *D. anitae*, *D. ferrea*, *D. kabuyeana*, *D. loureiriana* subsp. *loureiriana*, *D. lycioides* subsp. *sericea*, *D. mafiensis*, *D. mespiliformis*, *D. rotundifolia*, *D. mafiensis*, *D. mespiliformis*, *D. quiloensis*, *D. rotundifolia*, *D. squarrosa*, *D. usambarensis*, *D. verrucosa*, *D. villosa*, *D. villosa* var. *parvifolia*, *D. whyteana*, and *D. zombensis*. In addition, information is given on the part of the plant used as medicine, the manufacturing process of the traditional formulation, the main traditional therapeutic use, and the country from which the information originates.

The results show that 54.8% of the total *Diospyros* species from Mozambique are referred to for their traditional use (Table 2). Among these, *D. rotundifolia* (Figure 1), traditionally used to treat diarrhea [22], is a prevailing species of dense undergrowth in the coastal area of the Marracuene District [23].

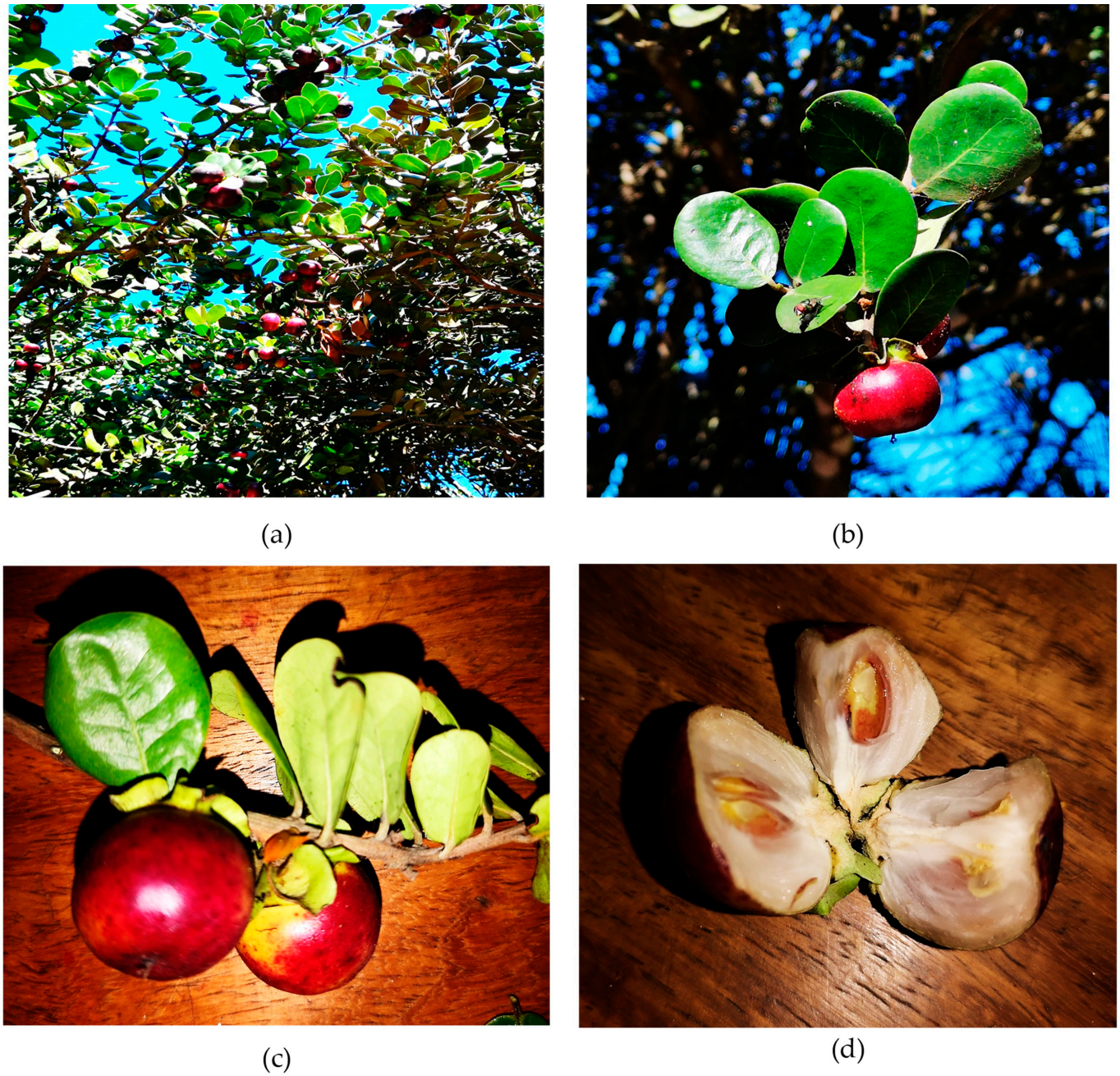


**Figure 1.** *Diospyros rotundifolia*: (**a**) aspect in its natural habitat; (**b**,**c**) details of leaf and fruit; (**d**) transverse view of the fruit with the seeds. Photography by Elsa Gomes.

Furthermore, among the *Diospyros* species present in the Mozambican flora, *D. villosa* (Figure 2) is a species with a well-established traditional use of both leaf [24] and root [25]; the latter mainly used as a toothbrush for hygiene purposes [26].

(**a**) (**b**)

**Figure 2.** *Diospyros villosa*: (**a**) Aspect in the natural habitat; (**b**) cross-section of the root. Photography by Elsa Gomes (**a**) and Adriana Ribeiro (**b**).

*Diospyros* species have been reported to be used to treat the signals and symptoms of over 20 diseases. Two of these species (*D. abyssinica* and *D. mespiliformis*) have been mentioned most frequently and are used in two to five different countries in Africa (Table 2).

Based on the diverse description in the literature for the human use of the different parts of *Diospyros*, the results are grouped into infectious diseases (antibacterial, antifungal, anthelminthic, and antiviral); gastrointestinal (diarrhea, dysentery, emetic, flatulence, and other gastrointestinal disorders), oral cavity (oral hygiene, healing of oral wounds, and toothaches); urogenital (anti-hemorrhagic, dysmenorrhea, and infertility); skin diseases (dermatitis, fresh wounds, bedsores, and rashes); musculoskeletal (body pain, bruises, painful fractures, and rheumatism); and others conditions (diabetes, internal injuries, antidotes, hemostatic agents, and snake bites).

Among all the different *Diospyros* plant parts used in traditional medicine (Figure 3), the root is the most-used part (82%, Figure 3a) and is most used to treat infectious diseases. In the treatment of gastrointestinal disorders, it corresponds to 59%, for oral cavity infections, 41%, and for skin diseases, 18%, as well as for the management of other conditions, comprising 12% (Figure 3b).

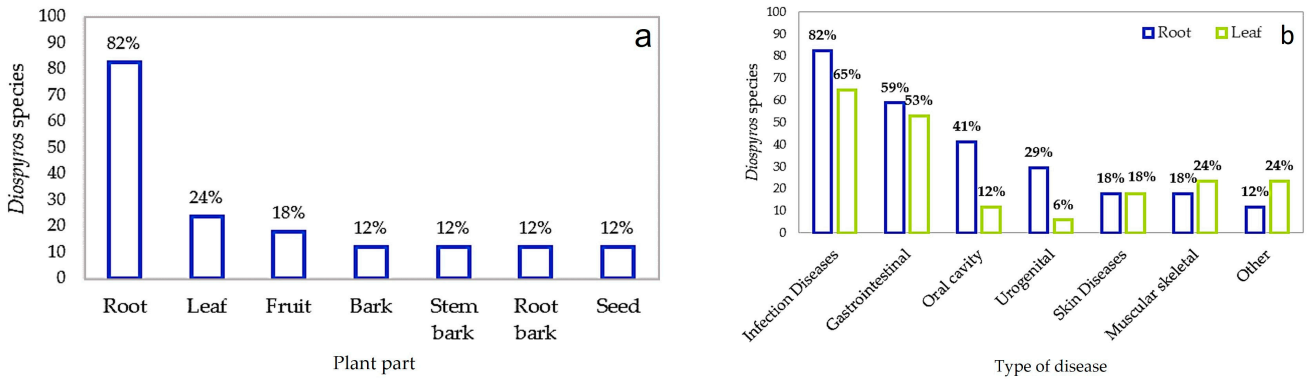


**Figure 3.** Traditional use of *Diospyros* species: (**a**) plant part used; (**b**) type of disease.

The leaf is the second-most used part of the *Diospyros* species, but it is used in a similar percentage (18%) to the root to treat skin conditions and more commonly (24%) for musculoskeletal bruises, painful fractures, body aches, and rheumatism (Figure 3a,b).

**Table 2.** Reported ethnomedical use of Mozambican *Diospyros* species.

| Species | Part Used | Preparation Method | Traditional Use | Country | Ref. |
|---|---|---|---|---|---|
| *D. abyssinica* | | | | | |
| | leaf | decoction | malaria<br>wound healing | Mali | [4,27] |
| | fruit (dry) | decoction | astringent and cholagogue<br>gastrointestinal disorders | | |
| | bark | unspecified | astringent and antipyretic<br>antihelminthic | | |
| | root | decoction | abdominal pain, dysentery, and diarrhea | | |
| | leaf<br>bark | juice | snake bite<br>astringent<br>internal injuries | Mali, Guinea<br>Zimbabwe | [28] |
| | bark | decoction | laxative<br>rash | Kenya | [29] |
| | leaf<br>seed | squeeze and apply | malaria and ringworm<br>ringworm<br>wound healing | Uganda | [30] |
| | leaf | juice | tropical ulcer (skin and soft tissue polymicrobial infection, feet, or lower legs localized) | | [31] |
| | tuber | decoction | upset stomach | | [32] |
| *D. anitae* | | | | | |
| | root | unspecified | dental hygiene<br>healing of oral wounds | Mozambique | [33] |
| *D. ferrea* | | | | | |
| | fruit | unspecified | diarrhea and sore throats<br>internal bleeding<br>renal lithiasis | India | [34] |
| | root | unspecified | anti-hemorrhagic<br>infertility | | [35,36] |
| | bark | | oral hygiene<br>skin diseases | | |
| *D. kabuyeana* | | | | | |
| | root | unspecified | antiviral | Tanzania | [37] |
| *D. loureiroana* subsp. *loureiroana* | | | | | |
| | root | chewing stick | oral hygiene | South Africa<br>East Africa | [4] |
| *D. lycioides* subsp. *sericea* | | | | | |
| | root bark | decoction | bloody feces<br>dysentery<br>headache | South Africa<br>South Central<br>Zimbabwe | [38–40] |
| | root | chewing stick | infertility | Namibia<br>Zambia | [41] |

**Table 2.** *Cont.*

| Species | Part Used | Preparation Method | Traditional Use | Country | Ref. |
|---|---|---|---|---|---|
| *D. mafiensis* | | | | | |
| | root | unspecified | diarrhea<br>leprosy<br>skin diseases (including fungal infections) | Mozambique<br>Tanzania | [42] |
| *D. mespiliformis* | | | | | |
| | leaf | decoction | analgesic and antipyretic<br>antihelminthic<br>dermatomycosis<br>fungal infections<br>induction of childbirth<br>hemostatic agent<br>malaria, pneumonia, and trypanosomiasis<br>sexually transmitted diseases<br>diarrhea and dysentery | Central<br>Southern<br>Eastern<br>Western<br>Africa | [27,43–47] |
| | leaf and bark | decoction | leprosy<br>oral infections<br>whooping cough | | |
| | leaf | decoction | bruises, bedsores, rash, and wounds<br>ringworm | | |
| | root | chewing stick | oral hygiene | | |
| | leaf, bark and root | decoction | toothache | Burkina Faso | [48] |
| | leaf | decoction | antipyretic<br>dermatitis<br>diarrhea and dysentery<br>malaria | | |
| | fruit | decoction | headache<br>pneumonia<br>rheumatism | Ghana | [27] |
| | stem bark | decoction | malaria and pneumonia | | |
| | root | decoction | infection with fever | | |
| | leaf | decoction | antipyretic<br>antidote for a variety of poisonous substances<br>diarrhea and dysentery<br>haemostatic agent<br>oral infections<br>wound healing | Nigeria | [49–51] |
| | root | decoction | malaria and oral candida infection (used as mouthwash, management of HIV/AIDS opportunistic diseases) | Zambia | [44,52] |
| | root | infusion | abdominal pain, body and heart pain | South Central Zimbabwe | [53] |
| | seed | unspecified | antibacterial | Guinea | [4] |
| *D. quiloensis* | | | | | |
| | stem bark | decoction | malaria<br>sexually transmitted diseases | Zambia | [44] |
| *D. rotundifolia* | | | | | |
| | root | not report | diarrhea | South African | [22] |
| *D. squarrosa* | | | | | |
| | root | not report | sexually transmitted diseases | Tanzania | [37] |

**Table 2.** *Cont.*

| Species | Part Used | Preparation Method | Traditional Use | Country | Ref. |
|---|---|---|---|---|---|
| *D. usambarensis* | | | | | |
| | root bark | unspecified | schistosomiasis | Malawi | [54] |
| | root | chewing stick | oral hygiene | Tanzania | [55,56] |
| | | decoction | fungal infections and overt symptoms of type 2 diabetes (i.e., polyuria, polydipsia, excessive thirst, and sweating) | | |
| *D. verrucosa* | | | | | |
| | root | unspecified | leprosy | Tanzania | [4,57] |
| *D. villosa* | | | | | |
| | leaf | unspecified | gastrointestinal disorders<br>painful fractures | South African | [24] |
| | root | decoction | gastrointestinal disorders<br>laxative<br>musculoskeletal system | Mozambique | [4,25,58] |
| | | toothbrush | oral hygiene | | |
| | | decoction | wounds (skin/subcutaneous tissue) | | |
| *D. villosa* var. *parvifolia* | | | | | |
| | leaf | infusion | emetic<br>antihelminthic | South Africa | [59] |
| | root | | emetic and flatulence<br>gastrointestinal disorders | | |
| *D. whyteana* | | | | | |
| | root | unspecified | antibacterial<br>dysmenorrhea<br>rash | South Africa | [60] |
| *D. zombensis* | | | | | |
| | root bark | unspecified | schistosomiasis | Malawi | [4,61] |

The majority of documented medicinal uses of *Diospyros* species are attributed to their effectiveness in treating microbial infections, encompassing bacterial, fungal, and parasitic infections. These include conditions such as diarrhea, dysentery, and various skin and oral cavity infections.

### 2.2. Chemical Composition of Mozambican Diospyros Species

The main classes of chemical constituents identified in *Diospyros* species from the Mozambican flora are listed in Table 3.

The presence of phenolic acid derivatives, like flavonoids and naphthoquinones (NQs), particularly 1,4-naphthoquinones (1,4-NQs), and terpenoids, mainly triterpenoids (especially lupan, ursane, oleanane derivatives) [3,4,17,62,63] and tetraterpenoids (carotenoids), have been reported [4]. Other chemical constituents in these *Diospyros* species include hydrocarbons, lipids, amino acids, and sugars [1,4,5,62].

**Table 3.** Chemical compounds identified in Mozambican *Diospyros* species.

| Species | Part Used | Chemical Class | Compounds | Extract | Ref. |
|---|---|---|---|---|---|
| *D. abyssinica* | | | | | |
| | root bark | naphthoquinone | plumbagin (2-methyl-5-hydroxy-1,4-naphthoquinone) | P. ether, CF, DCM, MeOH, $H_2O$, EtOH 80% MeOH | [28] |
| | stem bark | naphthoquinone | diospyrin, isodiospyrin | | [64,65] |
| | leaf | triterpenoid | betulinic acid, betulin and lupeol | | |

**Table 3.** *Cont.*

| Species | Part Used | Chemical Class | Compounds | Extract | Ref. |
|---|---|---|---|---|---|
| *D. consolatae* | | | | | |
| | n.r | triterpenoid | betulinic acid, betulin and lupeol | n.r | [4] |
| | n.r | naphthoquinone | diosindigo A | n.r | [4] |
| *D. dichrophylla* | | | | | |
| | seed | naphthoquinone | isodiospyrin | Hex | [66] |
| *D. ferrea* | | | | | |
| | leaf | triterpenoid | pregnenolone and androstan-6-one | MeOH | [67] |
| | n.r | | *β*-sitosterol | n.r | [4] |
| | leaf | monoterpenoid | citronellol | MeOH | [67] |
| | leaf | diterpenoid | phytol<br>thunbergol | MeOH<br>EtOAc | [67] |
| | leaf | triterpenoid | betulin, *α*-amyrin,<br>friedelan-3-one and olen-12-ene | EtOAc | [67] |
| | fruit | triterpenoid | friedelin, epifriedelinol, lupeol, lupenone, and betulin | n-Hex | [68] |
| | fruit | triterpenoid | *β*-sitosterol and stigmasterol | n-Hex | [68] |
| | root<br>fruit | naphthoquinone | 7-methyljuglone, isodiospyrin, diosindigo A and 8-hydroxyisodiospyrin | CF, n-Hex | [68,69] |
| | root | phenol | gallic acid | EtOH | [70] |
| | leaf | triterpenoid | friedelin, friedelin-3-ol, taraxerol and taraxerone | EtOH | [4] |
| | n.r | triterpenoid | ursolic acid | n.r | [4] |
| *D. inhacaensis* | | | | | |
| | stem | naphthoquinone | 7-methyljuglone and diospyrin | n.r | [71] |
| *D. kirkii* | | | | | |
| | n.r | triterpenoid | bauerenol, betulin and lupeol | n.r | [4] |
| | n.r | | *β*-sitosterol | n.r | [4] |
| | n.r | naphthoquinone | diosindigo A | n.r | [4] |
| *D. lycioides* | | | | | |
| | branche | naphthalene | Diospyroside A, B, C and D | MeOH | [72] |
| | | naphthoquinone | 7-methyljuglone and juglone | MeOH | [41] |
| | | triterpenoid | lupeol and ursolic acid | n.r | [53] |
| | fruit | naphthoquinone | isodiospyrin and bisisodiospyrin | n.r | [71] |
| | root, stem | naphthoquinone | 7-methyljuglone and isodiospyrin | CF | [71] |
| | n.r | naphthoquinone | mamegakinone, methylnaphthazarin and 8-hydroxyisodiospyrin | n.r | [4] |
| *D. mafiensis* | | | | | |
| | root bark | naphthoquinone | diosquinone, diosindigo A, 7-methyljuglone, 3-hydroxiquinone, and 6,8-bisdiosquinone | CF, DCM, MeOH | [42,73,74] |
| | stem bark | naphthoquinone | 7-methyljuglone and diosindigo A | | [73] |
| | leaf | triterpenoid | *α*-amyrin, lupeol and betulinic acid | CF, MeOH | [75] |
| | bark | naphthoquinone | diosquinone, isodiospyrin, and plumbagin | Ee | [4,52] |
| | stem bark | triterpenoid | lupeol, betulin, betulinic acid, *α*-amyrin, and bauerenol | CF | [4,76] |

**Table 3.** *Cont.*

| Species | Part Used | Chemical Class | Compounds | Extract | Ref. |
|---|---|---|---|---|---|
| *D. mespiliformis* | | | | | |
| | stem bark, leaf, bark | triterpenoid | betulinic acid, betulin, lupeol, bauerenol, and $\alpha$-amyrin | CF, MeOH | [4,76] |
| | leaf | flavonoid | 7-*O*-(4‴-*O*-acetyl)-allopyranosyl(1‴ → 2″)-$\beta$-glucopyranoside, along with eight flavonoid metabolites—luteolin 3′,4′,6,8-tetramethyl ether, luteolin 4′-*O*-$\beta$-neohesperidoside, luteolin 7-*O*-$\beta$-glucoside, luteolin, quercetin, quercetin 3-*O*-$\beta$-glucoside, quercetin 3-*O*-$\alpha$-rhamnoside, and rutin | n.r | [77] |
| | root | naphthoquinone | diosquinone, and plumbagin | P. ether | [78] |
| | root, bark | naphthoquinone | diospyrin | MeOH | [79] |
| | fruit | naphthoquinone | plumbagin | MeOH | [79] |
| *D. natalensis* | | | | | |
| | root, stem | naphthoquinone | 7-methyljuglone, and diospyrin | n.r | [4] |
| | n.r | triterpenoid | betulinic acid, $\alpha$-amyrin, and lupeol | n.r | [4] |
| | n.r | fatty acid | heptacosanoic acid | n.r | [4] |
| *D. quiloensis* | | | | | |
| | n.r | naphthalene | 4,5,6,8-tetramethoxy naphthaldhyde, 5-hydroxy-4,6,8-trimethoxy naphthaldehyde, 4,5,6-trimethoxynaphthalehyde, 4,5-dimethoxynaphthaldehyde, and 5-hydroxy-4-methoxy-2-naphthaldehyde | MeOH | [4] |
| *D. rotundifolia* | | | | | |
| | n.r | triterpenoid | betulin and lupeol | n.r | [4] |
| | root | naphthoquinone | 7-methyljuglone, neodiospyrin and rotundiquinone | n.r | [71] |
| | stem | naphthoquinone | 7-methyljuglone and diospyrin | n.r | [71] |
| *D. squarrosa* | | | | | |
| | n.r | naphthoquinone | 7-methyljuglone | n.r | [4] |
| *D. usambarensis* | | | | | |
| | root | naphthoquinone | 7-methyljuglone, isodiospyrin, diosindigo A and B, *bis*-isodiospyrin and mamegakinone | MeOH | [54,80] |
| | stem bark | naphthoquinone | 7-methyljuglone and diosindigo A | MeOH | [54] |
| *D. verrucosa* | | | | | |
| | root bark | naphthoquinone | diosindigo A, 7-methyljuglone, diosquinone and isodiospyrin | n.r | [57] |
| | root bark | triterpenoid | betulinic acid and betulin | | |
| | stem bark | naphthoquinone | diosindigo A, 7-methyljuglone, diosquinone and isodiospyrin | n.r | [57] |
| | stem bark | triterpenoid | betulinic acid and betulin | n.r | [57] |
| *D. whyteana* | | | | | |
| | n.r | naphthoquinone | 7-methyljuglone | n.r | [4] |
| *D. zombensis* | | | | | |
| | bark | triterpenoid | oleanolic acid | MeOH | [4] |
| | root bark | naphthoquinone | 7-methyljuglone, diosquinone, isodiospyrin and mamegakinona | P. ether, MeOH | [4,61] |

Extract: Ace—acetone; CF—chloroform; DCM—dichloromethane; Ee—ether; EtOAc—ethyl acetate; EtOH—ethanol; $H_2O$—water; Hex—hexane; MeOH—methanol; P. ether—petroleum ether; n.r—not reported.

Among the NQs (Figure 4), 80% are 1,4-NQs, either as monomers such as plumbagin (**1**) and 7-methyljuglone (**2**) or as dimers such as diospyrin (**3**) and isodiospyrin (**4**), while trimers and tetramers are less represented in this genus [4,81].

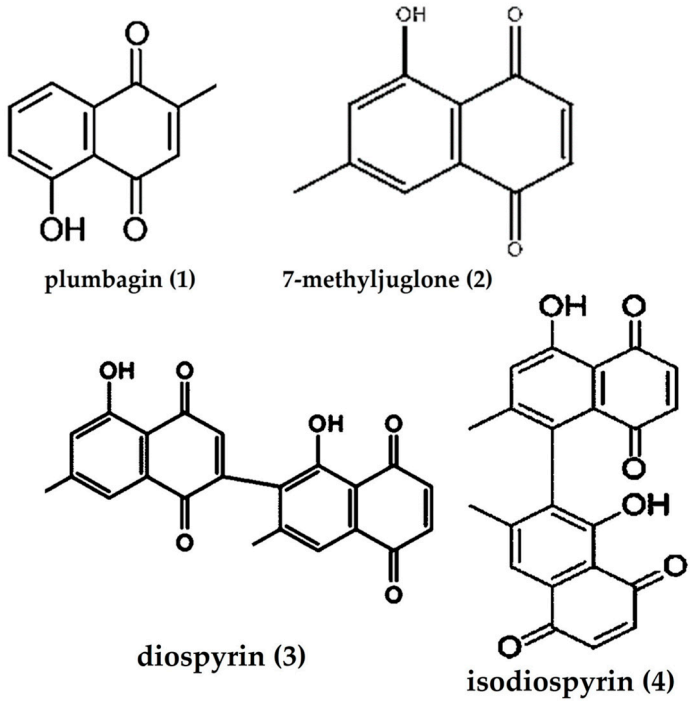


**Figure 4.** *Diospyros* representatives identified 1,4-naphthoquinones.

In the Mozambican *Diospyros* species, plumbagin (**1**) and 7-methyljuglone (**2**) are the most prominent 1,4-NQs identified [3,4]. The presence of 7-methyljuglone has been reported in diethyl ether, dichloromethane, chloroform, methanol, and hydroethanol extracts of the root, stem, and bark of most species [1,5] and in the ether extract of *D. lycioides* branches [41].

Plumbagin has been identified on the root bark of *D. abyssinica* [28], and isodiospyrin (**4**), a dimeric 7-methyljuglone derivative [3], has been reported in a hexane extract of *D. dichrophylla* seeds [66] and in the diethyl ether extract of bark and phylum of almost all Mozambican *Diospyros* species [4].

*D. mespiliformis* has been one of the best-studied Mozambican *Diospyros species*, having NQs identified in different plant parts [4,79] and triterpenoids in leaf, bark, and stem bark [4,76,82].

Triterpenoids (lupane, ursane, oleanane, taraxerane, and friedelane) are present in more than 90% of *Diospyros* species. Lupane-type compounds (Figure 5), such as betulinic acid (**1,** Figure 5), betulin (**2**, Figure 5), and lupeol (**3**, Figure 5), are the most active substances present in *Diospyros* African species [4,64,83,84]. These compounds were detected in different types of extracts (petroleum ether, dichloromethane, chloroform, methanol, hydroethanol, and aqueous extracts) and their fractions [1,5,28,41]. Several biological activities have been demonstrated for them, mainly for betulinic acid and its derivatives [83,85–88].

Condensed tannins (proanthocyanidins and oligopolymeric complex tannins), and particularly hydrolysable tannins (gallotannins, ellagitannins), and have also been identified in Mozambican *Diospyros* species such as *D. villosa* [4,25,58] and *D. mespiliformis* [82,89].

In addition, from the methanolic extract derived from *D. lycioides* twigs, three naphthalene glycosides were identified [72], and carotenoids were identified in the fruit of this species [90]. The presence of galactiol and vitamin E in the *D. ferrea* leaf was also reported [67].

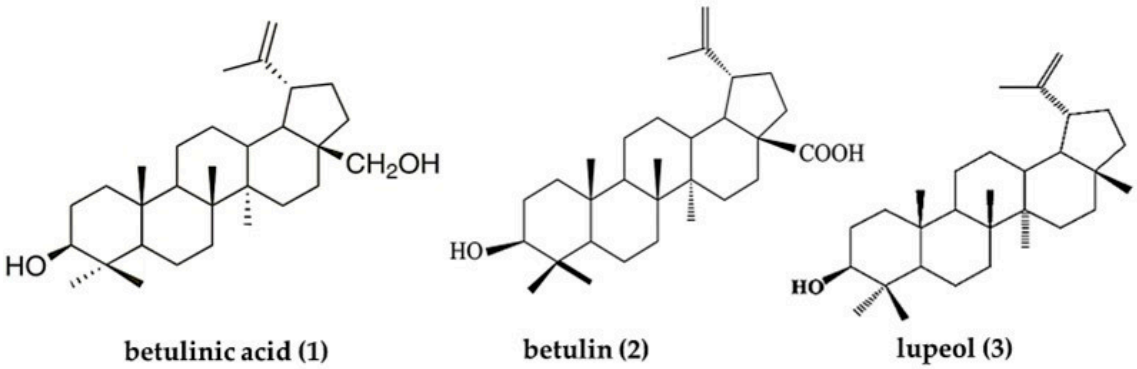


**Figure 5.** *Diospyros* identified representative lupan-type triterpenoids.

So far, the biologically active marker secondary metabolites isolated and studied from several species of the genus *Diospyros* have mainly been naphthoquinones, triterpenoids, and tannins. Compounds belonging to these chemical classes have been isolated from the twigs, bark, roots, leaves, stems, and fruits of Mozambican species of this genus. Examples include plumbagin, 7-methyljuglone, diospyrin, and isodiospyrin, which have been isolated from the root of several *Diospyros* species.

### *2.3. In Vitro and In Vivo Biological Activity of Mozambican Diospyros Species and Marker Compounds*

In Tables 4–6, the different in vitro and in vivo biological activities and toxicological tests performed on Mozambican *Diospyros* species, and their isolated marker secondary metabolites are summarized. A total of thirteen species (41.9%), namely *D. abyssinica*, *D. bussei*, *D. ferrea*, *D. kabuyeana*, *D. lycioides*, *D. loureiriana*, *D. mafiensis*, *D. mespiliformis*, *D. natalensis*, *D. squarrosa*, *D. usambarensis*, *D. verrucosa*, and *D. villosa*, were evaluated for biological activities other than antibacterial activities (Table 4).

#### 2.3.1. Anti-Inflammatory and Analgesic Activity

Aqueous extract of *D. abyssinica* root bark has shown stronger anti-inflammatory activity (enzyme 15-lipoxygenase (LOX) inhibition) than quercetin [27].

In vivo assays have shown that the hexane fraction of *D. mespiliformis* leaves has anti-inflammatory properties (inhibits stronger the LOX), and that the methanolic extracts of different plant parts showed wound healing effects. On the other hand, the butanol and ethyl acetate fractions activate LOX activity. These results show that *D. mespiliformis* extract can have pro-inflammatory and anti-inflammatory effects [51].

Lupeol isolated from *D. mespiliformis* stem bark has shown analgesic activity in both pain inhibition (neurological-first phase) and origin (inflammatory-second phase) in biphasic tests (in vivo) [76].

#### 2.3.2. Antihyperglycemic Activity

Another finding has revealed that the oral administration of a methanolic extract obtained from the leaves of *D. ferrea* (400 mg/kg) for a duration of 21 days in diabetic rats showed significant antihyperglycemic activity [91]. The root of this species is rich in phenolic acids, especially gallic acid, and is therefore traditionally used as a potent antioxidant [70].

#### 2.3.3. Antifungal Activity

Several studies have reported the potential antifungal activity of the root and root bark of most *Diospyros* species [42,54,92]. However, the antifungal activity of a leaf extract of *D. mespiliformis* has also been confirmed [47,93].

Various *Diospyros* medicinal plants are also effective against *Candida* spp. [1]. The methanolic extract of the *D. abyssinica* root is active against this microorganism [94]; how-

ever, in another study, it was only moderately active against the same microorganism [95]. Another medicinal plant, *D. mespiliformis*, is more active against *C. neoformans* than against *C. albicans*. A leaf extract showed anti-*C. albicans* activity, while a bark extract showed in vitro activity against *C. neoformans*-isolated strains from South African AIDS patients [96].

*D. mespiliformis*, traditionally used to treat ringworm, shows remarkable antimicrobial activity against *Trichophyton mentagrophytes* and *Microsporum canis*. This result supports the traditional use of this species against dermatophytosis [47]. Aqueous and ethanolic extracts of the leaf and bark of *D. mespiliformis* showed significant antifungal activity against *Aspergillus niger*, *Aspergillus flavus*, and *Microsporum gypseum* [97].

#### 2.3.4. Antiparasitic Activity

*Diospyros* species have antiparasitic activity, especially against both chloroquine-sensitive (3D7) and chloroquine-resistant (FcB1) strains of *Plasmodium falciparum* [31,94].

The decoction of the stem of *D. mespiliformis* was tested against *Plasmodium berghei*-infected mice and demonstrated potent activity, including the inhibition of beta-hematin in an in vitro study [98].

In vitro studies from methanolic extracts of *D. abyssinica* leaves have provided confirmation of its antiparasitic activity against *Leishmania donovani* [65,94], *Trypanosoma cruzi*, *Trypanosoma brucei* [99], *Culex*, and *Anopheles* larvae [94].

The isolated compound 7-methyljuglone obtained from the methanolic extract of *D. usambarensis* root bark has significant schistosomicidal activity [54,92].

#### 2.3.5. Antioxidant Activity

The scavenging activity of crude extract and fractions of four *Diospyros* species, namely *D. abyssinica*, *D. lycioides*, *D. mespiliformis*, and *D. villosa*, present in the Mozambican Flora was evaluated spectrophotometrically using the DPPH (1,1-diphenyl-2-picrylhydrazyl) radical assay.

An estimation of the concentration of antioxidant vitamins (i.e., A, C, and E) from crude methanolic extracts obtained from the leaf, bark, and root of *D. mespiliformis* was also determined using the DPPH [51].

**Table 4.** In vitro and in vivo non-antibacterial tests of biological activity in Mozambican species of *Diospyros* and marker compounds.

| Biological Activity/ Species | PU | Extract/ Compound | Results | Microorganism/ Assay | Control | Ref. |
|---|---|---|---|---|---|---|
| **Analgesic** | | | | | | |
| *D. mespiliformis* | SB | CF/lupeol 25 mg/kg, p.o | Pi[1] 2.2 ± 0.2/ asa =1.0 ± 0.3<br>Pi[2] 1.98 ± 0.1/ asa =1.15 ± 0.1 | Biphasic, Wistar rats | acetylsalicylic acid (asa), 100 mg/kg, p.o. | [76] |
| *D. ferrea* | L | CF<br>MeOH | 100–300 mg/Kg significant activity | Tail flick method, adult Wistar albino rats | ibuprofen | [100] |
| *D. ferrea* | R | CF<br>MeOH | 100–200 mg/Kg significant activity | Tail flick method, adult Wistar albino rats | ibuprofen | [101] |
| **Anti-inflammatory** | | | | | | |
| *D. abyssinica* | Rb | $H_2O$ (1)<br>MeOH (2) | 1—$IC_{50}$ = 16 ± 1 µg/mL<br>2—$IC_{50}$ = 86 ± 7 µg/mL | LOX, using soybean lipoxygenase type 1-B | quercetin, $IC_{50}$ value 11.5 ± 0.6 µg/mL | [27] |
| *D. ferrea* | L | CF<br>MeOH | 100–300 mg/Kg = 26.2–28.2%<br>100–300 mg/Kg = 29.6–37.6% | PIPE, adult male Wistar rats | ibuprofen 41.1% | [100] |
| *D. ferrea* | R | CF<br>MeOH | 100–200 mg/Kg = 37% | PIPE, adult Wistar albino rats | ibuprofen | [101] |
| *D. mespiliformis* | Sb | DCM Fraction maximally at 400 mg/kg | Modulation of serum concentrations of Tumour Necrosis Factor alpha and Interleukin 1 beta and 6 | Cytokine inhibition, *Plasmodium berghei*-infected mice | artemether-lumefantrine | [98] |
| | L | Hex Fraction<br>5 µg/mL(1)<br>10 µg/mL (2) | 1—$IC_{50}$ = 31.21 ± 0.84 µg/mL<br>2—$IC_{50}$ = 32.05 ± 2.79 µg/mL | LOX, Wistar rats | quercetin, $IC_{50}$ value<br>1–46.02 ± 5.46 µg/mL<br>2–32.05 ± 2.79 µg/mL | [51] |

**Table 4.** *Cont.*

| Biological Activity/ Species | PU | Extract/ Compound | Results | Microorganism/ Assay | Control | Ref. |
|---|---|---|---|---|---|---|
| **Antihyperglycemic** | | | | | | |
| *D. ferrea* | L | MeOH 21 days | 400 mg/kg, i.p, significant antihyperglycemic activity | Streptozotocin induced diabetic Wistar rats | glibenclamide, 0.5 mg/Kg, p.o. | [91] |
| **Antifungal** | | | | | | |
| *D. abyssinica* | R | MeOH | Actives in test controlled by conidial suspension | BA, *C. albicans* *C. cucumerinum* | methylthiazolyltetrazolium chloride (MTT) | [94] |
| *D. ferrea* | W | 1-isodiospyrin 2-plumbagin | 1—active against three fungi 2—active against eight fungi | HMBC | *Phomopsis* sp. reference spectrum for both H1 and C13 | [102] |
| *D. mafiensis* | Rb | 3-hydroxy-diosquinone | $MIC_{50}$ = 14.9 µg/mL $MIC_{50}$ = 39.1 µg/mL | CCA, *A. f*lavus, *A. parasiticus* | *A. parasiticus* B62 | [42] |
| | Rb | 3-hydroxy-diosquinone | Reduced total aflatoxin, 1.145 to 32 ng/plac | ELISA, *A. parasiticus*, *A. flavus* | *A. parasiticus* B62 | [42] |
| | Rb | diosquinone | $MIC_{50}$ > 100 µg/mL | CCA, *A. flavus*, *A. parasiticus* | *A. parasiticus* B62 | [42] |
| | Rb | diosquinone | Reduced total aflatoxin 1.145 to 45 ng/plac | ELISA, *A. flavus*, *A. parasiticus* | *A. parasiticus* B62 | [42] |
| | Rb | P. ether, DCM (E) Fraction (F) | E = 5 mg/disc IZ: 7–20 mm F = 0.2 mg/disc IZ: 19–20 mm | DD, *C. albicans* | miconazole 20 µg/disc IZ: 29 mm | [103] |
| *D. mespiliformis* | Rb L | Ace | MIC = 0.16 µg/mL | BD, *C. albicans*, *M. canis* | amphotericin B MIC = 0.02 µg/mL | [93] |
| | L | DCM:MeOH | MIC = 0.10–0.50 mg/mL | BD, *M. canis*, *T. mentagrophytes* | tetrazolium violet | [47] |
| | L | $H_2O$ | MIC = 0.08 µg/mL | BD, *M. canis* | amphotericin B MIC = 0.02 µg/mL | [93] |
| | B | Ace | IZ: 7 mm (1) IZ: 12 mm (2) | ADD, 1-*C. albicans*, 2-*C. neoformans* | nystatin | [96] |
| *D. usambarensis* | Rb | 7-methyljuglone | MIC = 0.025 µg/mL | BA, *C. cucumerinum* | miconazole MIC = 0.001 µg/mL | [92] |
| | Rb | isodiospyrin | MIC = 10 µg/mL | BA, *C. cucumerinum* | miconazole MIC = 0.001 µg/mL | [54] |
| *D. villosa* | R | EtOH 70% Fraction | MIC = 312.5 µg/mL MIC = 62.5–312.5 µg/mL | BD, *C. albicans* | not reported | [104] |
| **Antiparasitic** | | | | | | |
| *D. abyssinica* | L | EtOAc | $IC_{50}$ = 51.3 ± 8.8 µg/mL | BD, *P. falciparum* (FcB1) | chloroquine | [31] |
| | B | EtOAc | $IC_{50}$ = 1.5 µg/mL $IC_{50}$ = 5.6 µg/mL | *L. donovani* *P. falciparum* | pentamidine chloroquine | [65] |
| | B | diospyrin isodiospyrin | $IC_{50}$ = 0.5 µM | *L. donovani* | pentamidine $IC_{50}$ = 7 µM | [94] |
| | B | diospyrin isodiospyrin | $IC_{50}$ = 1.5 µM | *P. falciparum* (FcB1) | chloroquine $IC_{50}$ = 0.1 µM | [94] |
| | R | DCM MeOH | MIC = 500 mg/L | *Culex*, *Anopheles larvae* | not identified | [94] |
| *D. bussei* | R | MeOH | $IC_{50}$ = 65.7 ± 2.7 µg/mL | *T. brucei* (Lister 427) | pentamidine $IC_{50}$ = 0.000509 µM | [99] |
| *D. kabuyeana* | L | MeOH | $IC_{50}$ = 3.32 µg/mL | *T. brucei* (Lister 427) | pentamidine $IC_{50}$ = 0.000509 µM | [99] |
| *D. loureiriana* | Rb | MeOH | $IC_{50}$ = 1.68 ± 0.77 µg/mL | *P. falciparum* (3D7) | chloroquine $IC_{50}$ = 0. 0045 µM | [105] |
| | Sb | | $IC_{50}$ = 11.53 ± 1.99 µg/mL | | | [105] |
| | L | | $IC_{50}$ = 19.10 ± 4.41 µg/mL | | | [105] |
| *D. mespiliformis* | S | EtoAC (1) DCM (2) MeOHfraction (3) | 1—$IC_{50}$ = 3.18 µg/mL 2—$IC_{50}$ = 0.78 µg/mL 3—$IC_{50}$ = 0.55 µg/mL | *Plasmodium berghei*-infected mice | artesunate and chloroquine diphosphate | [98] |
| *D. natalensis* | Sb | MeOH | $IC_{50}$ = 2.85 µg/mL | *T. brucei* (Lister 427) | pentamidine $IC_{50}$ = 0.000509 µM | [99] |
| *D. squarrosa* | Rb | MeOH | $IC_{50}$ = 5.38 µg/mL | *T. brucei* (Lister 427) | pentamidine $IC_{50}$ = 0.000509 µM | [99] |

**Table 4.** *Cont.*

| Biological Activity/ Species | PU | Extract/ Compound | Results | Microorganism/ Assay | Control | Ref. |
|---|---|---|---|---|---|---|
| *D. verrucosa* | Sb | MeOH | $IC_{50}$ = 1.28 µg/mL | *T. brucei* (Lister 427) | pentamidine $IC_{50}$ = 0.000509 µM | [99] |
| | R | MeOH | $IC_{50}$ = 2.23 µg/mL | *T. brucei* (Lister 427) | | |
| | L | MeOH | $IC_{50}$ = 2.99 µg/mL | *T. brucei* (Lister 427) | | |
| *D. usambarensis* | Rb | 7-methyljuglone | Efficiency schistosomiasis MIC = 5 ppm | *Biomphalaria glabrata* | not identified | [54] |
| **Antioxidant** | | | | | | |
| *D. abyssinica* | Rb | EtOH (1) | 1-$EC_{50}$ = 16.0 ± 2 µg/mL | DPPH | quercetin $EC_{50}$ value 3.4 ± 0.3 µg/mL | [27] |
| | | MeOH (2) | 2-$EC_{50}$ = 16.6 ± 0.4 µg/mL | | | |
| | | $H_2O$ (3) | 3-$EC_{50}$ = 21 and 29 ± 2 µg/mL | | | |
| *D. lycioides* | L | Ace | *Rf* = 0.54; 0.60; 0.83; 0.89 | DPPH on TLC plates | phenolic compounds | [38] |
| *D. mespiliformis* | F | MeOH | 87.36% at 1 mg/mL | DPPH | vitamin E | [106] |
| | R | MeOH | $IC_{50}$ = 3.47 ± 0.05 µg/mL | DPPH | ascorbic acid | [51] |
| | F | MeOH | $IC_{50}$ = 6.94 ± 0.49 µg/mL | DPPH | 2.36 ± 0.30 µg/mL | [51] |
| | B | MeOH | $IC_{50}$ = 7.82 ± 0.76 µg/mL | DPPH | trolox 3.43 ± 0.78 µg/mL | [51] |
| | L | EtOAc Fraction | $IC_{50}$ = 1.08 ± 0.04 µg/ml | DPPH | ascorbic acid 5.08 ± 0.12 µg/mL | [51] |
| *D. villosa* | Sb | MeOH | $IC_{50}$ = 9.53 µg/mL | DPPH | ascorbic acid 10.3 µg/mL | [107] |
| | L | CF (1) | 1-$IC_{50}$ = 10.7 µg/mL | DPPH | ascorbic acid 10.3 µg/mL | [107] |
| | | Hex (2) | 2-$IC_{50}$ = 11.8 µg/mL | | | |

Part used (PU): L—leaf; B—bark; F—fruit; R—root; Rb—root bark; Sb—stem bark. Extract: Ace—acetone; ADD—agar disc diffusion; CF—chloroform; DCM—dichloromethane; EtOAc—ethyl acetate; EtOH—ethanol; $H_2O$—water; Hex—hexane; MeOH—methanol; P. ether—petroleum ether. Test: BA—TLC bioautography; BD—broth dilution; CCA—cell culture in agar; DD: disco diffusion method; DPPH—2,2-diphenyl-1-picrylhydrazyl; ELISA—enzyme-linked immunosorbent assay; HMBC—heteronuclear multiple-bond correlation method; PIPE—percent inhibition of paw edema. Abbreviations: LOX-15-lipoxygenase; $Pi^1$—pain inhibition (neurological-first phase); $Pi^2$—pain inhibition (inflammatory-second phase); EC50—half maximal effective concentration; IC50—half maximal inhibitory concentration; MIC—minimum inhibitory concentration.

### 2.3.6. Cytotoxicity, Genotoxicity, and Toxicity of Mozambican *Diospyros* Species

The results of in vitro cytotoxicity tests using normal and tumorous human cells and *Artemia salina*, as well as in vitro genotoxicity and in vivo acute and sub-chronic toxicity assessment of *Diospyros* species, are summarized in Table 5.

**Table 5.** In vitro cytotoxicity and genotoxicity studies as well as in vivo toxicity studies in Mozambican *Diospyros* species.

| Species | Parts Used | Extract | Toxicity Assay | Results | Ref. |
|---|---|---|---|---|---|
| *D. abyssinica* | | | | | |
| | leaf | EtOAc | Cytotoxicity against MRC-5 human diploid embryonic cells, Taxotere® as standard | $IC_{50}$ = 6.0 ± 5.0 µg/mL | [31] |
| | leaf | EtOAc | Cytotoxicity against KB human tumor cell lines (squamous cell carcinoma of the mouth), Taxotere® as standard | >85% cell inhibition $IC_{50}$ = 1.0 ± 2.0 µg/mL | [31] |
| | bark | EtOAc | Cytotoxicity against human KB cell (1) and *Rhabditis pseudoelongata* (2) | (1) $LD_{50}$ = 10 µg/mL (2) $LD_{50}$ = 1 µg/mL | [65] |
| *D. dichhropylla* | | | | | |
| | seed | DCM:MeOH (1) isodiospyrin (2) | Cytotoxicity using Brine shrimp test (*Artemia salina*) | 1-($LC_{50}$ = 29 µg/mL) 2-($LC_{50}$ = 0.13 µg/mL) | [66] |

**Table 5.** *Cont.*

| Species | Parts Used | Extract | Toxicity Assay | Results | Ref. |
|---|---|---|---|---|---|
| *D. ferrea* | | | | | |
| | leaf | MeOH | In vivo—acute oral toxicity using male Wistar albino rats | $LD_{50}$ = 2000 mg/kg | [91] |
| | fruit | isodiospyrin (1)<br>8′-hydroxyisodiospyrin (2) | Cytotoxicity strong against Hep-3B, KB, COLO-205, and HeLa cancer cells | 1($ED_{50}$ = 0.17, 1.72, 0.16 and 0.21 µg/mL)<br>2($ED_{50}$ = 1.31, 1.75, 1.96 and 1.79 µg/mL) | [68] |
| *D. lycioides* | | | | | |
| | leaf | Ace | Cytotoxicity against BUD-8 cell (human fibroblast cells) in real-time xCELLigence system and 7.4 µg/mL curcumin (control) | $IC_{50}$ = 500 and 1000 µg/mL | [38] |
| | leaf | Ace | Cytotoxicity against HeLa cells mobility assayed using the wound healing assay and 7.4 µg/mL curcumin (control) | Nontoxic to the normal cell at 300 µg/mL | [38] |
| *D. loureiriana* | | | | | |
| | root bark | MeOH | Cytotoxicity against human embryonic kidney cells (HEK293), estimated growth inhibition at 400 µg/ml | $IC_{50}$ = 100.34 ± 9.85 µg/mL | [105] |
| | stem bark | | | $IC_{50}$ = 57.26 ± 0.53 µg/mL | [105] |
| *D. mafiensis* | | | | | |
| | root bark | P. ether (1)<br>DCM (2)<br>EtOH (3)<br>fraction P. ether (4)<br>fraction DCM (5) | Cytotoxicity using brine shrimp larvae test (*Artemia salina*)<br>Standard cyclophosphamide $LC_{50}$ value of 17.78 µg/mL | 1-$LC_{50}$ = 25.12 µg/mL<br>2-$LC_{50}$ = 69.18 µg/mL<br>3-$LC_{50}$ = 120.23 µg/mL<br>4-$LC_{50}$ ≤ 8–45.71 µg/mL<br>5-$LC_{50}$ = 5.08 µg/mL | [103] |
| *D. mespiliformis* | | | | | |
| | stem bark<br>root bark | EtOH | In vivo—acute oral toxicity using Wistar rats of both sexes | $LD_{50}$ = 570 mg/kg<br>Acute toxicity is moderate | [49] |
| | leaf<br>stem bark | MeOH | in vivo—acute oral administration using rats | $LD_{50}$ ≥ 5 g/kg | [108,109] |
| | leaf<br>stem bark | EtOAc fraction | In vivo—sub-chronic toxicity using rats | $LD_{50}$ = 750 g/kg<br>$LD_{50}$ = 500 g/kg | [108] |
| | root | diosquinone | Cytotoxicity against human glioblastoma cell lines (1) and hormone-dependent human prostate cancer (2) | 1-$ED_{50}$ = 0.18 µg/mL<br>2-$ED_{50}$ = 4.50 µg/mL | [84] |
| *D. whyteana* | | | | | |
| | twigs | DCM | Genotoxicity against mutagens mitomycin C (MMC) using the Ames test (*Salmonella typhimurium* TA98) | protective effect non-genotoxic at 500–2500 µg/mL | [60] |
| | leaf | DCM<br>HydroMeOH 90% | Genotoxicity using the Ames test (*Salmonella typhimurium* TA98) | shift mutations of lowest dose is 0.50 µg/mL higher doses are toxic | [110] |
| *D. villosa* | | | | | |
| | root | HydroEtOH 70% | In vivo—acute toxicity using mice | possible renal dysfunction development | [58] |
| *D. zombensis* | | | | | |
| | root bark | 7-methyljuglone (1)<br>isodiospyrin (2) | Cytotoxicity against human colon carcinoma cells | 1-$LD_{50}$ of $7.0 \times 10^{-2}$ µg/mL<br>2-$LD_{50}$ of $3.8 \times 10^{-2}$ µg/mL | [61] |

Extracts: Ace—acetone; DCM—dichloromethane; EtOAc—ethyl acetate; EtOH—ethanol; $H_2O$—water; Hex—hexane; HydroEtOH—ethanol; HydroMeOH—methanol; MeOH—methanol; P. ether—petroleum ether. Concentration: $ED_{50}$—median effective dose; $IC_{50}$—half maximal inhibitory concentration; $LC_{50}$—lethal concentration 50%, $LD_{50}$—lethal dose 50%.

Most commonly, studies were found to be related to the in vitro assessment of cytotoxicity. For example, the extract of *D. lycioides* showed cytotoxicity to HeLa cells but was non-toxic to normal cells [38]. The compound diosquinone has been shown to be toxic against most cancer cell lines (human glioblastoma) and hormone-dependent human prostate cancer [84]. In contrast, 7-methyljuglone and isodiospyrin compounds are active against human colon carcinoma cells [61].

The organic extract of the inner seed of *D. dichrophylla* (Figure 6) is reported as highly cytotoxic ($LC_{50}$ = 29 µg/mL), particularly the isodiospyrin isolated from it ($LC_{50}$ = 0.13 µg/mL) [66].

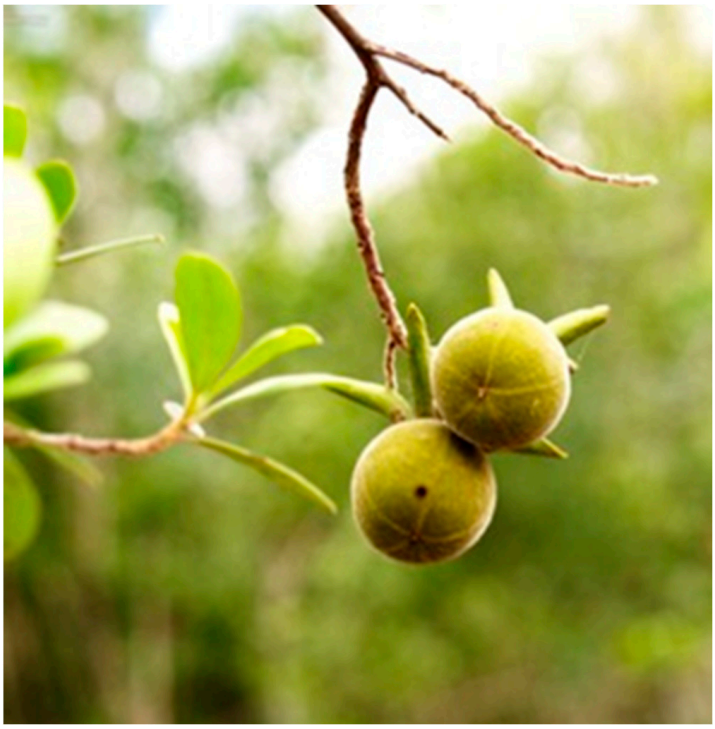

**Figure 6.** *Diospyros dichrophylla* (Gand.) De Winter: Detail of fruits in nature, Mandevo, Namaacha district, Maputo, 2010. Photography by Elsa Gomes.

Preclinical safety assessments of *Diospyros* species are of paramount importance; however, few studies related to Mozambican *Diospyros* species have been conducted to date. Cantrell et al. (2003) reported that *D. dichrophylla* is a potent phytotoxicant due to the presence of isodiospyrin (from the inner seed) at a lethal dose of 0.13 g/mL [66]. In another study, a hydroethanolic root extract of *D. villosa* showed possible development of renal dysfunction using an acute toxicity test in mice [111].

### 2.3.7. Antibacterial Activity

In vitro antibacterial activity data collected from eleven *Diospyros* species (representing 35.5% of the total) are summarized in Table 6. Of the 11 species examined, 47 extracts (including AgNPs) showed antimicrobial activity against multiple bacterial strains. The methanolic extract was the most tested. In some of the studies mentioned, biodirected fractionation was also performed, and the antibacterial activity of the obtained fractions and isolated compounds was determined. The results obtained are also shown in Table 6.

**Table 6.** In vitro antibacterial activity of Mozambican *Diospyros* and marker compounds.

| Species | Parts Used | Test | Extract/ Compound | MIC (µg/mL) | Microorganism | Control (MIC) µg/mL | Ref. |
|---|---|---|---|---|---|---|---|
| *D. abyssinica* | | | | | | | |
| | bark | BD | EtOAc | 12 | *S. aureus* ATCC 6538 | DMSO | [65] |
| *D. bussei* | | | | | | | |
| | leaf<br>stem bark | BD | MeOH | 125 | *E. coli* ATCC 8740 | ciprofloxacin 0.63 | [99] |
| | leaf | BD | MeOH | 8000 | *S. aureus* ATCC 25923<br>*B. cereus* ATCC 11775 | ciprofloxacin 2.5<br>ciprofloxacin 0.08 | |
| | root bark | BD | MeOH | 500 | *E. coli* ATCC 8740 | ciprofloxacin 0.63 | |
| *D. kabuyeana* | | | | | | | |
| | leaf | BD | MeOH | 8000 | *S. aureus* ATCC 25923 | ciprofloxacin 2.5 | [99] |
| | leaf | BD | MeOH | 4000 | *B. cereus* ATCC 11775 | ciprofloxacin 0.08 | |
| | stem bark | BD | MeOH | 1000 | | | |
| | leaf<br>stem bark | BD | MeOH | 125 | *E. coli* ATCC 8740 | ciprofloxacin 0.63 | |
| *D. lycioides* | | | | | | | |
| | branche | BD | MeOH | 1250 | *S. sanguis*, *P. gingivalis*, *S. mutans*, *P. intermedia* | alkaloid sanguinarine | [41] |
| | branche | BD | Diospyroside A | 39<br>78–1250 | *S. sanguis*, *P. intermedia*<br>*P. gingivalis*, *S. mutans* | alkaloid sanguinarine | [41] |
| | branche | BD | Diospyroside B | 39–78<br>156–625 | *S. sanguis*, *P. gingivalis*<br>*P. intermedia*, *S. mutans* | alkaloid sanguinarine | [41] |
| | branche | BD | Diospyroside C | 39–156<br>312–625 | *P. intermedia*, *S. mutans*<br>*P. gingivalis*, *S*, *sanguis* | alkaloid sanguinarine | [41] |
| | branche | BD | Diospyroside D | 156–312 | *S. mutans*, *P. intermedia*, *P. gingivalis*, *S. sanguis* | alkaloid sanguinarine | [41] |
| | branche | BD | juglone | 19–78<br>39 | *P. intermedia*, *S. mutans*, *S. sanguis*, *P. gingivalis* | alkaloid sanguinarine | [41] |
| | branche | BD | 7-methyljuglone | 39–156<br>78 | *P. gingivalis*, *S. mutans*<br>*S. sanguis*, *P. intermedia* | alkaloid sanguinarine | [41] |
| | leaf | BA | EtOAc<br>Ace | 0.10–0.16 *<br>0.12–0.17 * | *P. aeruginosa* ATCC 27853 | p-iodonitrotetrazolium chloride | [38] |
| | leaf | BA | EtOAc<br>Ace<br>MeOH | 0.16–0.36 *<br>0.20–0.45 *<br>0.16–0.27 * | *S. aureus* ATCC 29213 | p-iodonitrotetrazolium chloride | [38] |
| | leaf | BA | EtOAc<br>Ace<br>MeOH | 0.05–0.45 *<br>0.05–0.45 *<br>0.05–0.45 * | *E. faecalis* ATCC 29212 | p-iodonitrotetrazolium chloride | [38] |
| *D. mafiensis* | | | | | | | |
| | root bark | | DCM | *S. aureus*<br>*B. anthracis*<br>IZ: 12 mm | *S. typhi*, *S. boydii*, *E. coli*, *K. pneumoniae* *S. aureus*, *V. cholerae* *Proteus sp.*, *B. anthracis* | gentamycin ampicillin (20 µg/disc) | [103] |
| | root bark | | P. ether-Fraction | IZ: 10–15 mm | *S. typhi*, *S. boydii*, *E. coli*, *K. pneumoniae* *S. aureus*, *V. cholerae* *Proteus* sp., *B. anthracis* | gentamycin ampicillin (20 µg/disc) | [103] |
| *D. mespiliformis* | | | | | | | |
| | leaf | ADD | MeOH | 167 | *S. aureus* | isoniazid 5.0 | [50] |
| | root | ADD | MeOH | 250 | *S. aureus* | isoniazid 5.0 | [50] |
| | leaf | BD | EtOH | 12,500–25,000 | *Salmonella* spp., *Shigella* spp., *Campylobacter* spp. | ciprofloxacin, cefixime, and gentamicin | [95] |
| | leaf | BD | Hex (F1)<br>nBOH (F2)<br>EtOAc (F3)<br>$H_2O$ (F4) | (1)78.125–312.5<br>(2)156.25<br>(3)78.125–156.25<br>(4)625–2500 | 1-*P. aeroginosa*<br>2-*S. aureus*<br>3-*E. coli*<br>4-*S. typhimurium* | gentamicin 19.53<br>gentamicin 19.53<br>gentamicin 19.53<br>gentamicin 19.53 | [97] |
| | leaf | | | 625 | | | |
| | root | | | 625 (1)<br>>2500 (2 to 4) | | | |

**Table 6.** *Cont.*

| Species | Parts Used | Test | Extract/ Compound | MIC (µg/mL) | Microorganism | Control (MIC) µg/mL | Ref. |
|---|---|---|---|---|---|---|---|
| | leaf | AD | $H_2O$<br>HydroMeOH 10%<br>$H_2O$<br>HydroMeOH 10%<br>$H_2O$<br>HydroMeOH 10%<br>$H_2O$<br>HydroMeOH 10%<br>$H_2O$<br>HydroMeOH 10% | 250–500<br>125–500<br>125–250<br>62.5–125<br>250–250<br>125–125<br>250–250<br>125–125<br>250–500<br>125–250 | *H. influenzae* (6 ci)<br>*S. aureus* (5 ci)<br>*S. pneumoniae* (3 ci)<br>*S. pyogenes* (8 ci)<br>*M. catarrhalis* (5 ci) | ampicillin 0.12–15.6<br>ampicillin 0.06–0.12<br>ampicillin 0.015–0.12<br>ampicillin 0.015–0.06<br>ampicillin 0.12–1.9 | [112] |
| | leaf | BD | flavonol O-rhamnoside | 9770 | *S. aureus* | not identified | [77] |
| | root | AD | diosquinone<br>diosquinone | 3–30<br>15–16 | *S. aureus* NCT 6571<br>*S. aureus* E3T<br>*E. coli* KL16<br>*P. aeruginosa* NCT 6750 | ampicillin 5<br>gentamicin 2 | [78] |
| | leaf | DD | methylated flavone | IZ: 34 mm | *E. coli* | not identified | [78] |
| | leaf | AWD | EtOH-Fraction | IZ: 20 mm<br>IZ: 18 mm<br>IZ: 16 mm | *S. aureus*, *Shigella* spp.<br>*P. aeruginosa* | septrin 15 mm<br>spetrin 16 mm<br>spetrin 15 mm | [113] |
| *D. natalensis* | | | | | | | |
| | leaf | BD | MeOH | 250 | *S. aureus* ATCC 25923 | ciprofloxacin 0.08 | [99] |
| | leaf | | MeOH | 1000 | *B. cereus* ATCC 11775 | ciprofloxacin 2.5 | |
| | leaf | | MeOH | 500 | *E. coli* ATCC 8740 | ciprofloxacin 0.63 | |
| | root bark | | MeOH | 1000 | *E. coli* ATCC 8740 | ciprofloxacin 0.63 | |
| | stem bark | | MeOH | 250 | *E. coli* ATCC 8740 | ciprofloxacin 0.63 | |
| *D. rotundifolia* | | | | | | | |
| | not reported | | Ace | 230–1770 | *S. aureus*, *E. faecalis*, *E. coli* and *P. aeruginosa* | not reported | [22] |
| *D. squarrosa* | | | | | | | |
| | leaf | BD | MeOH | 4000 | *B. cereus* ATCC 11775 | ciprofloxacin 2.5 | [99] |
| | | | MeOH | 250 | *E. coli* ATCC 8740 | ciprofloxacin 0.63 | |
| | root bark | BD | MeOH | 1000 | *S. aureus* ATCC 25923 | ciprofloxacin 0.08 | |
| | | | MeOH | 4000 | *B. cereus* ATCC 11775 | ciprofloxacin 2.5 | |
| | stem bark | BD | MeOH | 500 | *E. coli* ATCC 8740 | ciprofloxacin 0.63 | |
| *D. verrucosa* | | | | | | | |
| | leaf | BD | MeOH | 1000 | *S. aureus* ATCC 25923 | ciprofloxacin 0.08 | [99] |
| | | | MeOH | 2000 | *B. cereus* ATCC 11775 | ciprofloxacin 2.5 | |
| | | | MeOH | 500 | *E. coli* ATCC 8740 | ciprofloxacin 0.63 | |
| | root bark<br>stem bark | BD | MeOH | <6.25 | *E. coli* ATCC 8740 | ciprofloxacin 0.63 | [82] |

**Table 6.** *Cont.*

| Species | Parts Used | Test | Extract/ Compound | MIC (µg/mL) | Microorganism | Control (MIC) µg/mL | Ref. |
|---|---|---|---|---|---|---|---|
| *D. villosa* | | | | | | | |
| | root | BD | HydroEtOH 70% | 62.5–312.5 | *E. faecalis* ATCC 435628 | not reported | [104] |
| | | | Ee | 15.6–62.5 | *E. coli* ATCC 25922 | not reported | |
| | | | Fractions | 31.2–62.5 | *M. luteus* ATCC 10240 | not reported | |
| | | | | | *S. aureus* ATCC 25923 | not reported | |
| | leaf | DD | AgNPs | IZ: 15 mm | *E. coli* ATCC 25922 | ciprofloxacin 37 mm gentamicin 20 mm | [107] |
| | | | AgNPs 80 °C | IZ: 18 mm | *S. aureus* ATCC 700698 | ciprofloxacin 6 mm gentamicin 11 mm | |
| | | | AgNPs | IZ: 16 mm | | | |
| | | | AgNPs | IZ: 16 mm | *S. epidermidis* ATCC 12228 | ciprofloxacin 28 mm gentamicin 20 | |
| | | | Ace | 0.05–0.45 * | | | |
| | | | MeOH | 0.05–0.45 * | | | |

Test: BD—broth dilution; DD—disc diffusion; ADD—agar disc diffusion; AWD—agar well diffusion. Extract: Ace—acetone; DCM—dichloromethane; Ee—ether; EtOAc—ethyl acetate; EtOH—ethanol; $H_2O$—water; Hex—hexane; HydroMeOH—methanol; nBOH—n-butanol; P. ether—petroleum ether. Strains: *B. anthracis*—*Bacillus anthracis*; *B. cereus*—*Bacillus cereus*; *E. faecalis*—*Enterococcus faecalis*; *H. influenzae*—*Haemophilus influenzae*; *K. pneumoniae*—*Klebsiella pneumoniae*; *M. catarrhalis*—*Moraxella catarrhalis*; *M. luteus*—*Micrococcus luteus*; *P. gingivalis*—*Porphyromonas gingivalis*; *P. intermedia*—*Prevotella intermedia*; *S. typhi*—*Salmonella typhi*; *S. typhimurium*—*Salmonella typhimurium*; *S. boydii*—*Shigella boydii*; *S. epidermis*—*Staphylococcus epidermidis*; *S. sanguis*—*Streptococcus sanguinis*; *S. mutans*—*Streptococcus mutans*; *S. pyogenes*—*Streptococcus pyogenes*; *V. cholerae*—*Vibrio cholerae*. Abbreviations: ATCC—American type culture collection, BA—TLC bioautography, ci—clinical isolate; IZ—zone of inhibition; MIC—minimum inhibitory concentration; AgNPs—silver nanoparticles; * Rf—retardation factor.

According to the WHO, oral diseases are the most common non-communicable diseases, affecting people throughout life and causing pain, discomfort, disfigurement, and even death [114]. The Global Burden of Disease Study reports that oral diseases are among the leading causes of health problems, estimating that half of the world's population is affected by these diseases [114,115]. The same study provided a comprehensive assessment, and among the results evaluated, permanent tooth decay was the most common cause, representing a major public health problem in many countries [116]. Therefore, preventing and controlling the spread of this health problem is a global challenge, requiring greater efforts and potentially innovative approaches to achieve it. The branches of several *Diospyros* (particularly *D. lycioides*, *D mespiliformis*, and *D. villosa)* are used as toothbrushes for oral care [41,44,52,104,117], and their plant extracts have been shown to be effective against common oral pathogens, including *Streptococcus mutans*, *S. sanguis*, periodontal pathogens (*Porphyromonas gingivalis* and *Prevotella intermedia*), *Lactobacillus* spp., and several strains of *Candida* spp. [41,44,52,104,117]. In fact, over the past few decades, the scientific community has become increasingly interested in understanding the versatility of medicinal plants from traditional herbal medicine and their guaranteed availability to improve clinical approaches to infectious diseases with the intention of reducing antimicrobial resistance [4].

### *2.4. Secondary Metabolites of Mozambican Diospyros Species as Potential Antimicrobial Agents*

#### 2.4.1. Naphtoquinones

Antibacterial Activity

Plumbagin (**1**, Figure 4) is recognized as an effective antibacterial agent against both Gram-positive and Gram-negative strains of bacteria. This compound has also shown significant inhibitory activity (MIC < 12.5 µg/mL) against the resistant strain of Mycobacterium tuberculosis H37Rv [3,78,118]. Plumbagin isolated from the bark extract of D. maritima and showed activity against S. aureus and Aeromonas hydrophila (MIC = 0.625 and 5 µg/mL, respectively) [119]. In addition, it has also been obtained from the root of D. mespiliformis and has been described as one of the active marker compounds as well as an effective antibacterial agent against Gram-positive and Gram-negative bacterial strains [50,77,112].

Another important compound isolated from *D. hebecarpa*, 7-methyljuglone (**2**, Figure 4), also present in the root of *Euclea natalensis* (*Ebenaceae*), is potentially active against *Mycobacterium tuberculosis* (H37Rv) [18].

Isodiospyrin (**4**, Figure 4), a dimeric 7-methyljuglone-derivative, has been reported to be more active than diospyrin (**3**, Figure 4) against various Gram-positive strains, including *Streptococcus pyogenes*, *S. pneumoniae*, *Corynebacterium diphtheriae*, *Bacillus subtilis*, *Listeria monocytogenes*, *Mycobacterium chelonae*, and *Micrococcus luteus*. Isodiospyrin demonstrates MIC values ranging from (0.78 to 50 μg/mL), while diospyrin shows MIC values ranging from (1.56 to 100 μg/mL) [17].

Extensive research has unveiled the mechanism of action of diospyrin and 7-methyljuglone against *M. tuberculosis*, highlighting their crucial role as non-competitive ATPase inhibitors in key enzymatic reactions [120]. Additionally, emerging evidence has demonstrated the anti-tuberculosis potential of other compounds, such as crassiflorone and plumbagin from *D. crassiflora*, as well as diospyrone and plumbagin from *D. canaliculata*, both derived from the stem bark [121].

In a study conducted by Kuete et al. (2010), it was demonstrated that isobavacalcone and diospirone, derived from *D. canaliculata*, show promise as potential drugs against multidrug-resistant Gram-negative strains. These compounds exhibited enhanced activity when used in combination with efflux pump inhibitors, resulting in MIC values decreased to <10 μg/mL [122,123].

### Antifungal and Antiviral Activities

The NQs have been well established, particularly against several species of *Candida*, infectious fungi of the mucosa, deep tissues, and the most common fungal diseases in HIV/AIDS patients [124]. Plumbagin inhibits the growth of *C. albicans*, *C. tropicalis*, and other fungi. In addition, fractions derived from plumbagin of *Diospyros* extracts are active against *C. albicans* [1]. In comparison with ketoconazole, a standard antifungal compound, plumbagin is considered a promising antifungal agent and has been used against *C. albicans*, *C. glabrata*, *C. krusei*, *C. tropicalis*, *Cryptococcus neoformans*, *Aspergillus niger*, *A. flavus*, *Alternaria* sp., *Cladosporium* sp., *Geotrichum candidum*, *Fusarium* sp., *Helminthosporum* sp., *M. gypseum*, and *Penicillium* sp. [125–127]. This compound, isolated from the stem bark of *D. bipindensis*, also exhibits significant activity against *C. albicans* [128–130].

Isolated from the root of *D. virginiana*, 7-methyljuglone and isodiospyrin have significant antifungal activity against *Phomopsis obscurans* (leaf blight), with 97.0% and 81.4% growth inhibition at 30 μM, respectively. These compounds also demonstrate activity against the pathogen *Phomopsis viticola*, with growth inhibition rates of 53.4% and 57.7%, respectively [131].

The antiaflatoxigenic activity of *D. mafiensis* root, another Mozambican medicinal plant, has been linked to the presence of diosquione and 3-hydroxydioquinone, making this herbal drug also an important natural antifungal for preventing fungal growth and aflatoxin accumulation in food [42]. In addition, this species has also been found to have analgesic, antidiabetic, anti-inflammatory, and antioxidant effects, likely correlated with the presence of these kind of constituents.

### Antiparasitic Activity

NQs are highly active against pathogens in neglected tropical diseases, including malaria, leishmaniasis, and trypanosomiasis (sleeping sickness). Studies examining *Plasmodium* sp. have shown that isodiospyrin-derived isodiospyrol A exhibits antimalarial activity ($IC_{50}$ = 2.7 μg/mL) [132]. Anti-plasmodial activity has also been reported in the ethanolic extract of leafs of *D. monbuttensis* ($IC_{50}$ = 3.2 nM) [133]. Studies on malaria have proposed a redox cycling mechanism (described for the novel antimalarial–antiparasitic drug atovaquone) to support the in vitro activity of diospyrin and its analogues isolated from *D. montana* against *L. donovani* [134].

Plumbagin and its derivative was shown to be active against *Leishmania* spp., while diospyrin was active against *Leishmania donovani* [87]. Semisynthetic crassiflorone derivatives display trypanocidal activity against *T. brucei* and *T. cruzi* [135]. Antiplasmodial activities with $IC_{50}$ values of 16.5 to 29.4 g/mL against chloroquine-sensitive (3D7) and chloroquine-resistant (K1) strains of *P. falciparum* were observed for the juglone-based 1,4-NQs present in *D. sylvatica* [136].

Concerning the assessment of anthelmintic activity, it was demonstrated in vitro that *D. oocarpa*, *D. nigrisence*, *D. candolleana*, and *D. montana* are active on adult earthworms of *Pheritima posthuma* [137]. Similarly, NQ derivatives, including diospyrin from *D. oocarpa*, *D. nigrisence*, and *D. candolleana*, are antiprotozoal in addition to possessing anthelmintic constituents [138].

#### 2.4.2. Triterpenoids

##### Antibacterial and Antifungal Activities

Betulinic acid isolated from the root of *D. lotus* presents a broad spectrum against several Gram-positive and Gram-negative bacteria [85,139–141]. Betulin isolated from *D. rubra* is an active agent against *Streptococcus pyogenes*, with a MIC of 85 µg/mL, and *Corynebacterium diphtheriae*, with a MIC range of 64 to 256 µg/mL [88].

Methanolic extract obtained from *D. peregrina* bark and seed containing triterpenoids has been studied for its antidiarrheal properties [142]. Similarly, the methanolic extract of *D. peregrina* fruit showed high activity against *E. coli* (12.6 mm zone of inhibition) and against fungi *C. albicans* (10.7 mm zone of inhibition) and *Penicillium* spp. (7.33 mm) [143].

Betulin present in the hexane fraction isolated from the bark of *D. paniculata* is very efficient against *S. dysenteriae*, which is responsible for diarrhea (MIC = 30 µg/mL) [144]. However, a study of a reductive green synthesis of nano-sized Ag particles using methanolic root extracts of *D. paniculata* showed that the maximum activity was displayed against Gram-positive bacteria compared to Gram-negative bacteria. The maximum activity was observed against *Penicillium notatum*, *A. flavus*, and *Saccharomyces cerevisiae*, with moderate activity towards *C. albicans* and *A. niger* [145].

In another study of ursane-type triterpenoids obtained from the leaf of *D. dendo* Welw. Ex Hiern [EtOH−EtOAc (50:50) extract], antimicrobial activity (62% at 10 µg/mL) against *Pseudomonas aeruginosa* was observed. This Gram-negative bacterium is considered one of the three main causes of human opportunistic infections and has recently been a useful model for the study of biofilm formation, implying antimicrobial resistance to antibiotics [146].

##### Antiviral Activity

Structure–activity relationships between betulinic acid and its synthetic derivatives inhibiting HIV-1 replication, HIV-1 entry, and HIV-protease or reverse transcriptase (RT) have been verified [147,148]. Betulinic acid was identified as a highly promising antiviral (anti-dengue) present in high proportions in most extracts of distinct species of *Diospyros*, particularly from the bark of *D. glans* [83]. Aridanin, isolated from methanol extracts obtained from the leaf, stem, and root of *D. conocarpa*, presents anti-HIV-1IN activity [149].

In a recent study, the antiviral activity of *D. anisandra* was demonstrated against the influenza virus AH1N1pdm09. The *n*-hexane fruit extract exhibited HA inhibitory (HAI) activity, and a fraction of it inhibited the hemagglutination from 12.5 up to 100 µg/mL, which was attributed to the synergistic effect of the different compounds present [150]. Previously, possible antiviral activity against influenza A and B viruses has been attributed to a redox effect of isolated zeylanone epoxide [151].

##### Antiparasitic Activity

Using in vitro antimalarial assays, betulinic acid 3-caffeate isolated from the dried leaf, twig, and branch of *D. quaesita* was shown to be moderately active against both chloroquine-sensitive and chloroquine-resistant *P. falciparum* clones [86]. Lupeol and lupenone, isolated

from the dichloromethane and ethyl acetate extracts of *D. rubra* stem, have shown moderate antimalarial activity against *P. falciparum* [88]. On the other hand, hydroethanolic extracts from the trunk of *D. gracilescens* and the hexane fraction showed higher activity against promastigote and amastigote forms of *L. donovani* ($IC_{50}$ = 5.84 µg/mL and $IC_{50}$ = 0.79 µg/mL, respectively) [87]. Aridanin isolated from methanol extracts of the leaf, stem, and root of *D. conocarpa* can be sources of new antitrypanosomal active principles [149].

#### 2.4.3. Tannins

Tannins isolated from Mozambican *Diospyros* species represent an important class of secondary metabolites with remarkable antimicrobial potential against fungi, bacteria, and yeast [152]. Their mechanism of action involves the disruption of microbial enzymes and cell membranes, although their activities are diverse [153]. In addition, recent research has suggested the ability of tannins to generate hydrogen peroxide, which contributes to their important antibacterial properties [154].

##### Antibacterial and Antifungal Activities

*D. melanoxylon* bark is another medicinal plant considered to be active against Gram-positive and Gram-negative bacteria, which is traditionally used for diarrhea, urinary, and skin troubles and has confirmed claims against *E. coli*, *S. aureus*, *S. epidermidis*, *Shigella flexneri*, *Bacillus licheniformis*, *Bacillus brevis*, *Vibrio cholerae*, *P. aeruginosa*, *Streptococcus aureus*, *Candida kruesi*, and *Bacillus subtilis* [155]. Furthermore, it shows promise in the treatment of candidiasis caused by different *Candida* species (*C. viz*, *C. albicans*, *C. krusei*, *C. parapsilosis*, and *C. tropicalis*), with MIC values ranging from 0.375 to 6.0 mg/mL [156]. Extracts derived from the bark of *D. melanoxylon* are rich in tannins and possess significant potential as antimicrobial agents. In a recent study using strains isolated from humans, it was effective against both Gram-positive and Gram-negative bacteria, suggesting the presence of a broad spectrum of antibiotic compounds or simply general metabolic toxins in the plant methanolic extract [157,158]. In another study conducted in India, acetone ethyl acetate and methanol extracts of *D. melanoxylon* showed a MIC < 30 µg/mL against *Aeromonas hydrophila*, *Enterobacter aerogenes*, *E. coli*, and *Klebsiella pneumoniae* [159].

Methanol extract obtained from the bark or seed of *D. peregrina*, which is rich in tannins and other phenols, was evaluated for its antibacterial potential against the pathogenic bacteria associated with diarrhea. The bark extract demonstrated inhibitory effects against *S. aureus*, *Shigella dysenteriae*, *E. coli*, and *P. aeruginosa*, while the seed extract inhibited all tested strains except for *P. aeruginosa* [160]. Similarly, the methanol extract of *D. tricolor* leaves, known for its abundance of tannins and other phenols, exhibited antibacterial activity against both Gram-positive bacteria (*Bacillus cereus* and *S. aureus*) and Gram-negative bacteria (*Salmonella typhii* and *Escherichia coli*) [161].

*Diospyros kaki* Thunb., known as the persimmon tree, is originally from Asia, but it is cultivated in various parts of the world, including Mozambique. Different plant parts are well-known and useful as medicinal plants, and the fruit is known as persimmon. This species has been extensively studied, particularly regarding the antimicrobial activity of the tannins isolated from it. In a study conducted by Liu et al. (2019), the antimicrobial effects of persimmon tannins (PTs) extracted from the fruit of *D. kaki* against methicillin-resistant *Staphylococcus aureus* (MRSA) were investigated. The persimmon tannins (MIC = 1000 µg/mL) displayed potential mechanisms of inhibitory activity (i.e., the tannins can change the normal morphology of MRSA and cause severe damage to the cell wall and cell membrane) [152]. In addition, the hydrolysate of condensed tannins (composed of a polymer of flavan-3-ols, such as catechin groups) exhibited high bacteriostatic activity in vitro against the *M. avium* complex (nontuberculous mycobacteria) that causes opportunistic chronic pulmonary infections [63]. Aqueous extract from the *D. kaki* fruit was tested in vivo, showing interesting antibacterial activities against Gram-negative strains compared to Gram-positive bacteria, justifying its use in traditional medicine for the treatment and/or management of disorders of the digestive system such as diarrhea [162].

The results of another study showed that the condensed tannins extracted from the unripened fruit of *D. kaki* displayed antibacterial activity against biofilms containing multiple bacteria. It is estimated that intraoral cavity biofilms consist of at least 800 types of bacteria. Therefore, it is suggested that this medicinal plant has a high potential for preventing dental disease and aspiration pneumonitis in geriatric patients and recovering patients when it is added to mouthwash and toothpaste [163].

The in vitro antibacterial potential of *D. blancoi* was also found against biofilm formation by *S. mutans*. Both extracts containing tannins and other phenols showed inhibition ranges of 96% for methanol and 95% for ethyl acetate [164].

Recently, *Diospyros* species rich in tannins have been applied in the development of nanoparticles. For instance, titanium dioxide ($TiO_2$) nanoparticles containing *D. ebenum* leaf extract exhibit excellent antibacterial activity and potential against Gram-negative bacteria *E. coli* [165]. Silver nanoparticles (AgNPs) containing aqueous extract from the fruit of *D. malabarica* have demonstrated antibacterial activity against *S. aureus* at 500 µg/mL and against *E. coli* at 1000 ug/mL, with an average zone of inhibition size of 8.4 ± 0.3 mm and 12.1 ± 0.5 mm and 6.1 ± 0.7 mm and 13.1 ± 0.5 mm, respectively [166]. Similarly, biogenic silver nanoparticles demonstrated excellent antibacterial activity against a broad range of bacteria, with the highest antibacterial activity observed against *E. faecalis* (17.77 mm) and *B. subtilis* (20 mm), also demonstrating good hemocompatibility against humans and rat red blood cells [167].

### Antiviral Activity

No studies were found on the specific activity of tannins isolated from the native *Diospyros* species in Mozambique. However, a tannin isolated from *D. kaki* has been demonstrated to have in vitro antiviral activity against the influenza virus, vesicular stomatitis virus, poliovirus, coxsackievirus, adenovirus, rotavirus, feline calicivirus, mouse norovirus, Sendai virus, and Newcastle disease virus [168]. The results of another study involving *D. kaki* extracts with tannin contents ranging from 0.08 to ≥0.11 mg/mL demonstrated their capacity to inactivate human noroviruses and bacteriophage MS2, both of which are the cause of gastroenteritis and foodborne illnesses worldwide (i.e., the results suggest that the antiviral effect and astringent effects of tannins are likely related to noroviral genome reduction and MS2 inactivation) [169].

### Antiparasitic Activity

Species of the genus *Diospyros* contain a broad spectrum of antimicrobial agents identified using in vitro and/or in vivo methods against strains capable of causing opportunistic infections as well as neglected parasitic diseases. The anthelmintic activity of a *D. peregrina* fruit extract containing tannins was compared to the standard drug albendazole. The extract was found to be more potent than the selected standard drug at a concentration of 10 mg/mL [170].

According to the WHO, malaria is one of the most widespread neglected diseases in Africa, caused by the parasite *Plasmodium* and responsible for severe immune complications and deaths. The anti-*Plasmodium* activity of extracts from various species of the Mozambican *Diospyros* species has been reported in the literature. Ethyl acetate extract from *D. abyssinica* leaves showed moderate activity against chloroquine-resistant *Plasmodium falciparum* (FcB1), while *D. mespiliformis*, traditionally used to treat malaria, showed potent antimalarial activity in mice infected with *Plasmodium berghei* and significant inhibition of beta-hematin using an in vitro assay [98].

The antiparasitic activity against *Leishmania donovani*, *Trypanosoma cruzi*, and *Trypanosoma brucei* was confirmed in several studies on *Diospyros* species [99]. For example, an acetate leaf extract of *D. abyssinica* and the isodiospyrin and diospyrin marker compounds isolated from the bark by bioguided fractionation showed high anti-*L. donovani* activity ($IC_{50}$ = 1.5 g/mL, extract, and $IC_{50}$ = 0.5 g/mL, isolated compounds) [65].

## 3. Materials and Methods

This review was conducted according to the criteria described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (http://www.prisma-statement.org/; accessed on 16 January 2023). For this purpose, the scientific literature data were considered until 10 December 2022.

### *3.1. Search Strategy*

The scientific data were collected using the search engines PubMed, Scopus, Web of Science, and Google Scholar, identifying all scientific papers published between 1 January 1970, and 10 December 2022 using the keywords Diospyros AND antibacterial, Diospyros AND antifungal, Diospyros AND antiparasitic, Diospyros AND antiviral, Diospyros AND medicine, Diospyros AND chemical compounds, Diospyros AND biological activity, and Diospyros AND toxicity.

### *3.2. Study Selection*

As described in Figure 7, a total of 5528 scientific studies were included in the search and initial data collection based on their title and abstract. After eliminating the duplicates, 2071 studies remained, of which 1852 could not be selected due to a lack of information relevant to this work. After the screening, 279 studies reporting on *Diospyros* were considered eligible for inclusion in this review.

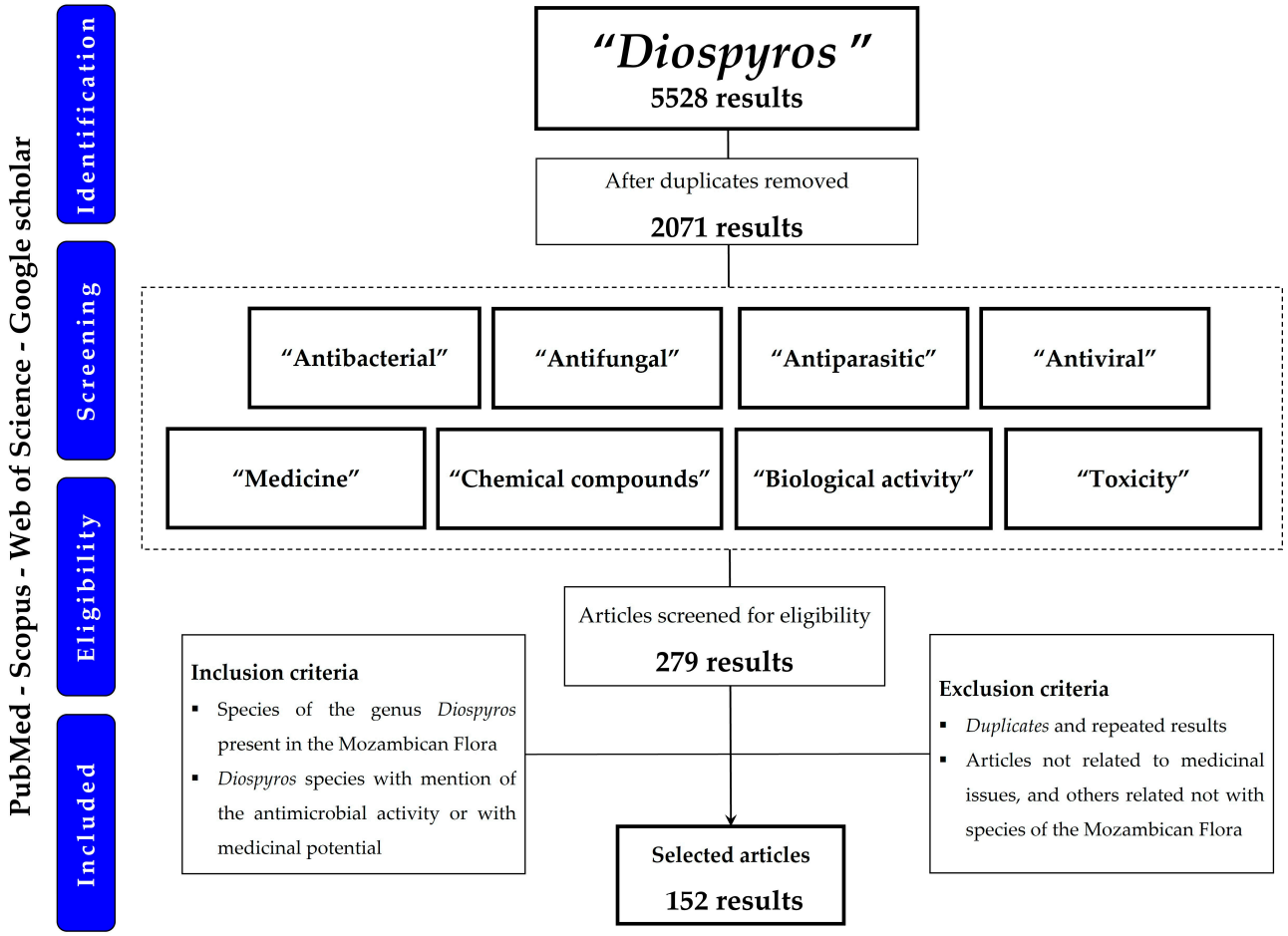


**Figure 7.** PRISMA flowchart of the screening process in the different databases.

3.2.1. Criteria for Inclusion and Exclusion of Data

Inclusion Criteria

- Related to the *Diospyros* genus, in particular species of the genus *Diospyros* present in Mozambican Flora;
- Abstract or full text in English;
- Studies on *Diospyros* species concerning their medicinal importance.

Exclusion Criteria

- Duplicate scientific publications;
- Not directly related to medicinal issues and others related but not with species of Mozambican Flora;
- Containing irrelevant or incomplete information.

## 4. Conclusions

Species of the genus *Diospyros* have been studied worldwide, with a significant number exhibiting pharmacological activity. One referenced example, *D. kaki*, native to East Asia, NaoXinQing, is part of a patented and officially approved traditional Chinese medicine formula for the treatment of stroke. However, there are no studies integrating data on all *Diospyros* species present in the flora of Mozambique.

More than 70% of Mozambique's population uses medicinal plants for primary health care, and a total of 54.8% of the *Diospyros* species used in the country's ethnomedicine are also used in other regions of Africa; however, the biological potential of most of them is still largely unknown. For example, 64.5% of these species were not tested for their antibacterial properties, namely *D. abyssinica* subsp. *attenuata*, *D. abyssinica* subsp. *Chapmaniorum*, *D. anitae*, *D. consolatae*, *D. consolatae-rotundifolia intermediates*, *D. dichrophylla*, *D. ferrea*, *D. inhacaensis*, *D. kirkii*, *D. kirkii-mespiliformis intermediates*, *D. loureiriana* subsp. *Loureiriana*, *D. natalensis* subsp. *Numulária*, *D. quiloensis*, *D. senensis*, *D. truncatifolia*, *D. usambarensis* subsp. *Usambarensis/rufescens*, *D. villosa* var. *parvifolia*, *D. villosa* var. *villosa*, *D. whyteana*, *D. zombensis*, and *Diospyros* sp. no. 1 sensu FZ. On the other hand, several isolated compounds of these species (particularly naphthoquinones and triterpenoids) have also been isolated from other species of the genus *Diospyros*, showing different biological activities including antiviral activity. However, no antiviral studies were found on the Mozambican species.

Studies on the antifungal potential of *Diospyros* are still scarce. In fact, the antifungal activity of 98.14% of the species (*D. abyssinica* subsp. *attenuata*, *D. abyssinica* subsp. *chapmaniorum*, *D. anitae*, *D. bussei*, *D. consolatae*, *D. consolatae-rotundifolia intermediates*, *D. dichrophylla*, *D. inhacaensis*, *D. kabuyeana*, *D. kirkii*, *D. kirkii-mespiliformis intermediates*, *D. loureiriana* subsp. *loureiriana*, *D. lycioides* Desf. subsp. *sericea*, *D. natalensis* subsp. *natalensis*, *D. natalensis* subsp. *numulária*, *D. quiloensis*, *D. rotundifolia*, *D. senensis*, *D. squarrosa*, *D. truncatifolia*, *D. verrucosa*, *D. villosa* var. *parvifolia*, *D. whyteana*, *D. zombensis*, and *Diospyros* sp. No. 1 sensu FZ) need to be evaluated, as they are traditionally used to treat skin diseases and diseases of the oral cavity, as well as other diseases where opportunistic fungal infections can co-occur. In addition, antiparasitic activities have been studied in other species of the genus *Diospyros*, however, 97.21% of Mozambican species (*D. abyssinica* subsp. *attenuata*, *D. abyssinica* subsp. *chapmaniorum*, *D. anitae*, *D. consolatae*, *D. consolatae-rotundifolia intermediates*, *D. dichrophylla*, *D. ferrea*, *D. inhacaensis*, *D. kirkii*, *D. kirkii-mespiliformis intermediates*, *D. lycioides* Desf. subsp. *sericea*, *D. mafiensis*, *D. natalensis* subsp. *numularia*, *D. quiloensis*, *D. rotundifolia*, *D. senensis*, *D. squarrosa*, *D. truncatifolia*, *D. villosa* var. *villosa*, *D. villosa* var. *parvifolia*, *D. whyteana*, *D. zombensis*, and *Diospyros.* sp. no. 1 sensu FZ) have not yet had their antiparasitic activities studied.

In summary, out of the 31 native and naturalized species in the flora of Mozambique that are used in different regions of Africa, a total of 17 species have not been studied as antimicrobial agents, of which three species, namely *D. dichrophylla*, *D. whyteana*, and *D. zombensis*, have only been studied at the toxicological level. Of the 14 species that have

already been the subject of antimicrobial studies, *D. abyssinica* and *D. mespiliformis* are the best studied.

This work provides comprehensive information on the chemical, biological, and toxicological studies of the *Diospyros* species present in the flora of Mozambique, examining their pharmacological potential in detail. Of the *Diospyros* plant parts, the root is the best-researched and documented. The identified studies confirmed ongoing efforts to improve the understanding of the mechanism of action underlying the biological activity, and in particular, the antimicrobial activity of these species, drawing on their traditional use. In addition, several secondary metabolites of *Diospyros* are currently being investigated for their potential pharmacological applications. However, it is important to emphasize that most of the available data are in vitro assessments of biological activity. Therefore, further efforts are needed to obtain more comprehensive evidence aimed at strengthening the validity and applicability of the results and ultimately contributing to public health benefits, especially in the face of global antimicrobial resistance.

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