An overview of the phytochemistry of medicinal bark (trunk, stem or root) from the most popular southern African species

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Abstract The ten countries that make up southern Africa are collectively a hot-spot of medicinal plant knowledge, with a unique preference for the utilization of bark over leaves from possibly hundreds of species. The most popular 86 medicinal bark species were identified in an earlier survey of various muthi markets around Johannesburg, and are listed in the current review, out of which chemical data was found for 63 and tabulated. The chemistry of medicinal bark species is, however, incomplete, since many scholars focused their research on metabolites of interest to their research groups, such as essential oils, lipophilic compounds, alkaloids or saponins, to the exclusion of other specialized metabolites present in the respective biota. From the current phytochemical analysis, the medicinal potential of bark relative to leaves is not obvious, as it is dependent on factors such as quantity of specialized metabolites (potency), their identities and anecdotal accounts from traditional healers. Nevertheless, the preference for bark may be due to empirical outcomes in therapy. Southern African medicinal bark species demonstrate an extremely diverse pool of unique/new or relatively unheard of natural products, such as calondendrolide from *C. capense*, combretastatin from *C. caffrum*, capensin from *C. capense*, crotohalimaneic acid from *C. sylvaticus*, ekebergins from *E. capensis*, entandrophragmin from *E. caudatum*, lysisteisoflavone from *E. lysistemon*, kigelinone from *K. africana*, holstinones from *O. holstii*, piptadeniaoside from *P. africanum*, rauvolfianoids from *R. caffra*, tetrapterosides from *T. tetraptera*, voacangine from *V. thouarsii*, warburganal from *W. salutaris* and mucronine from *Z. mucronata*. The review concludes by briefly commenting on pharmacokinetic aspects associated with ingestion or topical application of bark metabolites.

Keywords Bark · Medicinal bark · Phytochemistry · Southern Africa

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Introduction

Bark is defined as all external tissues that surround the vascular cambium, occupying a much smaller volume as compared to the wood. This is mostly because wood tissue is preserved for structural maintenance of the organism, while the outermost bark cells are

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continuously discarded. The outer bark is non-living tissue, and the living inner bark is external to vital cells, making it an adequate site for the accumulation of specialized metabolites to levels above those tolerated by internal tissues (Hon and Shiraishi 2000). Hence, bark is a suitable site for the elimination of metabolites from the organism, conveniently creating a barrier to phytopathogens and herbivores, but in traditional medicinal practice it serves as a reservoir of bioactive products.

In traditional medicinal practice, selection of tree, stem or root bark over leaves is common. In such cases bark was determined to be superior to other organs, via iterative trial and error selection. Medicinal bark species are used in all cultures across the world, for example, the Egyptians and Sumerians utilized the bark of willow (*Salix* spp.) and poplar (*Populus* spp.) trees, containing salicin and salicylic acid respectively (Norn et al. 2009), and the South Americans utilized bark from *Cinchona,* containing quinine (Permin et al. 2016). There are also ethnobotanical records of medicinal bark use from Australia (Lassak and McCarthy 2011), China (Kopp et al. 2003), Thailand (Phumthum et al. 2018) and India (Biswas and Mukherjee 2003), just to name a few.

Southern Africa represents a hot-spot of medicinal bark selection and chemical diversity (Khumalo 2018; Khumalo et al. 2021). Research on the chemistry of the various bark species used in traditional practice demonstrates that they contain a diverse array of unique, novel, or new specialized metabolites, ranging from polar to non-polar ingredients, belonging to multiple classees of compound, alkaloids, terpenes, flavonoids, phenylpropanoids, phenols and many more.

In comparing the accumulation of specialized metabolites in bark against leaves, the taxonomic level is most important in determining differences between the levels, yields or concentration of specialized metabolites. There are several examples from Lamiaceae (Sadgrove et al. 2020b) or Scrophulariaceae (Sadgrove et al. 2011, 2021; Sadgrove and Jones 2014a) where leaves (not bark) accumulate volatile organic compounds at yields ranging from 1 to 8% of the fresh weight. In another example, it is the fruit of *Maclura pomifera* (Rafinesque) Schneider that accumulate the highest yield of the prenylated flavonoids, osajin and pomiferin at nearly 1% (Tsao et al. 2003).

However, there are many other examples of metabolite accumulation in bark or wood pulp that greatly exceeds the density in leaves. For example, the accumulation of tryptamines in the bark of *Mimosa tenuiflora* (Willd.) Poir. (syn. *Mimosa hostilis* Benth.) far exceeds the content in the leaves (Pilar Nicasio et al. 2005). In another example, the wood pulp of *Artocarpus heterophyllus* Lam., yielded 1% of the prenylated isoflavone artocarpin, significantly higher than the concentration in leaves (Morrison et al. 2021).

The yield of specialized metabolites is not always why there is a preference for bark in *Materia medica* selection of specific taxa. In most cases, chemical differences between leaves and bark are the reason for the differences of therapeutic attributes, and this is evident in a significant number of phytochemical studies. In the published literature, the vast majority of plant-organ comparisons are made between essential oils from bark and leaves, such as in studies of *Pinus* (Bagci et al. 2011), *Cinnamomum* (Singh et al. 2007), or *Boswellia* (Geetha and Chakravarthula 2018). But mass spectral and NMR studies are also available that compare the various plant organs and identify chemical dissimilarities among the non-volatile metabolites, such as in fruits of *Aesculus* (Green et al. 2021), bark and leaves of *Flindersia* (Picker et al. 1976), and the same for *Ficus* (Ramadan et al. 2009).

While such comparisons are not available for the majority of medicinal bark species of southern African origin, chemical data from bark is regarded as independent of the chemistry of leaves for reasons mentioned above. Therefore, the identities of metabolites in the bark of medicinal-bark species is considered more relevant to the discussion of therapeutic outcomes than the comparison between plant organs. In the current narrative, the specialized metabolites of popular southern African bark medicines are summarised and discussed in the context of human health, using information from published sources.

Materials and methods

The most popular medicinal bark species were identified from previous work (Khumalo 2018; Khumalo et al. 2021) and via a search of the published literature. A popular species is defined as one that is traded in commerce. While there are many more medicinal bark species, they are not traded in the muthi markets, so

they are not regarded as popular. To obtain chemical data of medicinal bark species, google scholar was used and the search phrases were "genus," "species," "bark," and "chemistry." The accepted names, genus and species, were determined by searching plants of the world online, Kew, and synonyms were also used in the literature search. Exclusion criteria included studies only of leaves or wood pulp, or studies that used qualitative phytochemical assays, or only thin layer chromatography, and not more up to date methods. Inclusion criteria were for studies of bark, either stem, tree or root bark.

Results

By focusing on the most popular medicinal bark species in southern Africa, a list of 86 medicinal bark species were compiled (Table 1). The vast majority of these were identified by Khumalo (2018) and Khumalo et al. (2021), and details related to usage modalities and targeted ailments are provided in their studies. English vernacular names are provided, as are the Zulu names, which are the names used in muthi market trade. Out of the 86 listed in Table 1, chemical data of specifically the bark of either root, stem or tree, was found for 63 species (Table 2).

The chemical data listed in Table 2 (bark of either root, stem or tree) is limited to the metabolites of interest to the authors of the chemical studies. This leaves open many avenues for further research. Authors that focused on alkaloids neglected to study terpenes or flavonoids, and so on. Some studies also focused on essential oils only, or characterized the chemistry using LC–MS and spectral identification, so the data in Table 2 should not be considered complete. Nevertheless, the chemical data is comprehensive, since much of it was determined through chromatographic isolation and assignment by nuclear magnetic resonance spectroscopy.

A chemical overview of medicinal bark species in southern Africa conveys that there is a high chemical diversity across species, with no patterns or salient features that identify them as bark per se. Several of the species contain previously undescribed compounds that were named according to their etymological connection to the genus or species. Examples include the furanosesquiterpene lactone calondendrolide (**1**) from *C. capense* (Kiprop et al. 2005), the stilbene combretastatin (**2**) from *C. caffrum* (Pettit et al. 1987), the coumarin capensin (**3**) from *C. capense* (Okwemba et al. 2018), the halimane diterpene crotohalimaneic acid (**4**) from *C. sylvaticus* (Maroyi 2017), the ekebergin limonoid (**5**) from *E. capensis* (Irungu et al. 2014), the limonoid entandrophragmin (**6**) from *E. caudatum* (Ansell and Taylor 1988), the prenylated isoflavone lysisteisoflavone (**7**) from *E. lysistemon* (Sadgrove et al. 2020a), the furanonapthaquinone kigelinone (**8**) from *K. africana* (Gupta and Jain 2019), the holstinone sterol (**9**) from *O. holstii* (Kalenga et al. 2021), the pentacyclic triterpene saponin piptadeniaoside (**10**) from *P. africanum* (Noté et al. 2013), the indole rauvolfianoid alkaloid (**11**) from *R. caffra* (Bitombo et al. 2022), the pentacyclic triterpene monoglucosides called tetrapterosides (**12**) from *T. tetraptera* (Noté et al. 2009), the methoxylated indole alkaloid methyl ester voacangine (**13**) from *V. thouarsii* (Goldblatt et al. 1970), the sesquiterpene dialdehyde warburganal (**14**) from *W. salutaris* (Khumalo et al. 2019b) and the macrolide mucronine (**15**) from *Z. mucronata* (Auvin et al. 1996; Barboni et al. 1994). These examples capture the diversity of metabolite profiles across species (Figs. 1, 2).

While medicinal bark of southern Africa is chemically diverse, there are also several compounds that are somewhat ubiquitous across the plant kingdom, such as the sterols and triterpenes, including lupeol, the amyrin isomers, sitosterol, ursolic acid and oleanolic acid. These triterpenes are often at the core of more complex structures, such as saponins (with complex patterns of sugars bonded). Other relatively ubiquitous compounds belong to the flavonoids class, such as catechin, apigenin and quercetin, as well as phenols, such as ellagic acid, gallic acid or benzoic acid (including derivatives). Fatty acids are infrequently reported, but this may be due to the disinterest across the science community. Fatty acids are frequently ignored in spectroscopic studies due to their lack of novelty, but often include palmitic acid, linoleic acid, stearic acid or oleic acid.

Discussion

While medicinal bark selection is of high cultural importance to the people of southern Africa, conservationists have been exploring the potential impact on

Table 1 The 86 most popular medicinal bark species used in southern Africa, most of which are available in the Johannesburg muthi markets and prescribed by herbal practitioners

Genus	Species	Authority (Family)	Zulu	English vernacular	Chemical data (yes/no)
Albizia	*Adianthifolia*	(Schumach.) W.Wight (Fabaceae)	Umgadankawu	Flat-crown tree	Yes
Araucaria	*Heterophylla*	(Salisb.) Franco (Araucariaceae)	Abangqongqozi	Monkey puzzle	Yes
Balanites	*Maughamii*	Sprague (Zygophyllaceae)	Iphamba	Torchwood	Yes
Berchemia	*Discolor*	(Klotzsch) Hemsl. (Rhamnaceae)	Uvuka	Bird plum	Yes
Bersama	*Lucens*	(Hochst.) Szyszyl. (Melianthaceae)	Undiyaza	Glossy bersama	Yes
Bersama	*Swinnyi*	E. Phillips (Melianthaceae)	Undiyaza	Glossy white ash	Yes
Bersama	*Tysoniana*	Oliv. (Melianthaceae)	Undiyaza	Common white ash	No
Bobgunnia	*Madagascariensis*	(Desv.) J.H. Kirkbr. et Wiersema	No record found	Snake bean plant	Yes
Brackenridgea	*Zanguebarica*	Oliv. (Ochnaceae)	Mutavhatsindi	Yellow peeling plane	Yes
Bridelia	*Micrantha*	(Hochst.) Baill. (Phyllanthaceae)	Umhlahle/umhlahla	Coastal goldenleaf	Yes
Calodendrum	*Capense*	(L.f.) Thunb. (Rutaceae)	Umemezi omhlophe	Cape chestnut	Yes
Carissa	*Bispinosa*	(L.) Desf. Ex Brenan (Apocynaceae)	Umvusankunzi	Num-num	No
Cassine	*Papillosa*	(Hochst.) Kuntze (Celastraceae)	No record found	No record found	Yes
Cassipourea	*fFanaganii*	(Schinz) Alston (Rhizophoraceae)	Umemezi obomvu	Cape onionwood	Yes
Cinnamomum	*Camphora*	(L.) J.Presl (Lauraceae)	Uloselina	Camphor tree	Yes
Combretum	*Caffrum*	(Eckl. & Zeyh.) Kuntze (Combretaceae)	Isidubu	Cape bushwillow	Yes
Commiphora	*Africana*	(A. Rich.) Engl. var. africana (Burseraceae)	Iminyela	Hairy corkwood	Yes
Croton	*Gratissimus*	Burch. (Euphorbiaceae)	Isikhumampuphu	Lavender croton	Yes
Croton	*Sylvaticus*	Hochst. (Euphorbiaceae)	Umahlabekufeni	Forest fever-berry	Yes
Cryptocarya	*Latifolia*	Sond. (Lauraceae)	Umkhondweni	Broad-leaved laurel	Yes
Cunonia	*Capensis*	L. (Cunoniaceae)	Umlulama	Butterspoon tree	No
Curtisia	*Dentata*	(Burm.f.) C.A.Sm. (Curtisiaceae)	Umlahleni	Assegai-tree	No
Dichrostachys	*Cinerea*	(L.) Wight & Arn. (Fabaceae)	Ugagane	Sicklebush	Yes
Dombeya	*Rotundifolia*	(Hochst.) Planch. (Malvaceae)	Unhliziyonkulu	Wild pear	Yes
Ekebergia	*Capensis*	Sparm. (Meliaceae)	Umnyamathi/Umathunzin' entaba	Cape ash	Yes
Elaeodendron	*Croceum*	(Thunb.) DC (Celastraceae)	Lisithundu	Common saffron	No

Table 1 continued

Genus	Species	Authority (Family)	Zulu	English vernacular	Chemical data (yes/no)
Elaeodendron	*Transvaalensis*	(Burtt Davy) R.H.Archer (Celastraceae)	Ingwavuma	Transvaal saffronwood	Yes
Entandrophragma	*Caudatum*	(Sprague) Sprague (Meliaceae)	Umgugudo	Bushveld saffron	Yes
Eriocoelum	*Microspermum*	Radlk. ex De wild. (Sapindaceae)	No record found	No record found	Yes
Erythrina	*Lysistemon*	Hutch. (Fabaceae)	Umnsinsi	Common coral tree	Yes
Erythrophleum	*Lasianthum*	Corbishley (Fabaceae)	Umbhemiso/umkhwangu	Swazi ordeal tree	No
Eucalyptus	*Sideroxylon*	A.Cunn. Ex Wools (Myrtaceae)	Umdlavuza	Red ironbark	Yes
Euclea	*Natalensis*	A.DC. (Ebenaceae)	Isizimane	Natal guarri	Yes
Ficus	*Glumosa*	Delile (Moraceae)	Inkokhokho	Mountain rock fig	Yes
Garcinia	*Gerrardii*	Harv. Ex Sim (Clusiaceae)	Umbinda	Forest mangosteen	Yes
Garcinia	*Lvingstonei*	T. Anderson (Clusiaceae)	Igobandlovu	African mangosteen	Yes
Haplocoelum	*Accuminatum (syn. congolanum)*	Radlk. Ex Engl. (Sapindaceae)	No record found	No record found	Yes
Harpephyllum	*Caffrum*	Bernh. (Anacardiaceae)	Umgwenya	Wild plum	Yes
Heteromorpha	*Arborescens*	(Spreng.) Cham. & Schltdl. (Apiaceae)	Umbangandlala	Tropical parsley	No
Hippobromus	*Pauciflorus*	(L.f.) Radlk. (Sapindaceae)	Isiphahluka	False horsewood	No
Ilex	*Mitis*	(L.) Radlk. (Aquifoliaceae)	Xidumo/udumaphansi	African holly	No
Kigelia	*Africana*	(Lam.) Benth. (Bignoniaceae)	Umvongothi	Sausage tree	Yes
Lannea	*Schweinfurthii* var. *stuhlmannii*	(Engl.) Engl. var. *stuhlmannii* (Engl.) Kokwaro (Anacardiaceae)	Umganunkomo	False-marula	Yes
Macaranga	*Capensis*	(Baill.) Sim (Euphorbiaceae)	Unompumelelo	River macaranga	Yes
Maytenus	*Undata*	(Thunb.) Blakelock (Celastraceae)	Undabulavalo	Koko tree	Yes
Ochna	*Holstii*	Engl. (Ochnaceae)	Isibhanku	Red ironwood	Yes
Ocotea	*Bullata*	(Burch.) Baill. (Lauraceae)	Unukani	Black stinkwood	Yes
Olax	*Obtusifolia*	De Wild. (Olacaceae)	No record found	Large-fruited olax	Yes
Ozoroa	*Paniculosa*	(Sond.) R.Fern & A.Fern (Anacardiaceae)	Isifice/isifuce	Common resin tree	No
Pappea	*Capensis*	Eckl. & Zeyh (Sapindaceae)	Iletha, umhuluka	Jacket plum	No
Peltophorum	*Africanum*	Sond. (Fabaceae)	Msehla/umsenhla	African-wattle	Yes
Philenoptera	*Volacea*	(Klotzsch) Schrire (Fabaceae)	Isihomohomo	Apple-leaf	No
Piptadeniastrum	*Africanum*	(Hook.f.) Brenan (Fabaceae)	No record found	African greenheart	Yes
Pleurostylia	*Capensis*	(Turcz.) Loes. (Celastraceae)	Umthunyelwa	Bastard saffronwood	No

Table 1 continued

Genus	Species	Authority (Family)	Zulu	English vernacular	Chemical data (yes/no)
Protorhus	*Longifolia*	(Bernh.) Engl. (Anacardiaceae)	unhlangothi	Red-beech	Yes
Prunus	*Africana*	(Hook.f.) Kalkman (Rosaceae)	Inyazangoma elimnyama	Stinkwood	Yes
Ptaeroxylon	*Obliquum*	(Thunb.) Radlk. (Rutaceae)	Umthathe	Sneeze wood	Yes
Pterocarpus	*Angolensis*	DC. (Fabaceae)	Umvangazi	Bloodwood	Yes
Pterocelastrus	*Rostratus*	Walp. (Celastraceae)	Usehlulabanye/ Usehlulamanye	Red candlewood	No
Rapanea	*Melanophloeos*	(L.) Mez (Primulaceae)	Umaphipha	Cape beech	No
Rauvolfia	*Caffra*	Sond. (Apocynaceae)	Umhlambamanzi	Quinine tree	Yes
Schotia	*Brachypetala*	Sond. (Fabaceae)	Umgxamu/ihluze	Weeping boer-bean	No
Sclerocarya	*Birrea*	(A. Rich.) Hochst. (Anacardiaceae)	Umganu	Marula	Yes
Searsia	*Chirindensis*	(Baker.f.) Moffett (Anacardiaceae)	Inyazangoma elibomvu	Red current	No
Securidaca	*Longepedunculata*	Fresen (Polygalaceae)	Mpesu/ iphuphuma	Violet tree	Yes
Securidaca	*Welwitschii*	Oliv. (Polygalaceae)	No record found	No record found	Yes
Sideroxylon	*Inerme*	L. (Sapotaceae)	Amasethole	White milkwood	Yes
Spirostachys	*Africana*	Sond. (Euphorbiaceae)	Umthombothi	Tamboti	Yes
Strychnos	*Henningsii*	Gilg (Loganiaceae)	Umqalothi	Red bitter berry	Yes
Syzygium	*Cordatum*	Hochst. Ex Krauss (Myrtaceae)	Umdoni	Water berry	Yes
Terminalia	*Catappa*	L. (Combretaceae)	No record found	Indian almond	Yes
Terminalia	*Sericea*	Burch. ex DC. (Combretaceae)	Amangwe	Silver cluster-leaf	Yes
Terminalia	*Superba*	Engl. & Diels. (Combretaceae)	Mususu (Venda)	Silver cluster-leaf	Yes
Tetrapleura	*Tetraptera*	(Schumach. & Thonn.) Taub. (Fabaceae)	No record found	Aridan	Yes
Trichilia	*Dregeana*	Sond. (Meliaceae)	Umathunzini	Forest mahogany	No
Trichilia	*Emetica*	Vahl (Meliaceae)	Umkhuhlu	Natal mahogany	No
Turraea	*Floribunda*	Hochst. (Meliaceae)	Umadlozane	Honeysuckle-tree	Yes
Turraea	*Obtusifolia*	Hochst. (Meliaceae)	Ikunzi	Small honeysuckle tree	No
Vachellia	*Natalitia*	(E.Mey.) Kyal. & Boatwr. (Fabaceae)	Umunga	Pale-barked sweet thorn	No
Vachellia	*Robusta*	(Burch.) Kyal. & Boatwr. subsp. robusta (Fabaceae)	Umngamanzi	Broadpod robust thorn	No
Vachellia	*Xanthophloea*	(Benth.) Banfi & Galasso (Fabaceae)	Umkhanyakude	Fever tree	Yes
Vitex	*Obovata*	E.Mey. (Verbenaceae)	Umluthu	Hairy finger leaf	No

Table 1 continued

Genus	Species	Authority (Family)	Zulu	English vernacular	Chemical data (yes/no)
Voacanga	*Thouarsii*	Roem. & Schult (Apocynaceae)	Indlabalozi/indlabaloyi	Wild frangipani	Yes
Warburgia	*Salutaris*	(G. Bertol.) Chiov. (Cannellaceae)	Isibhaha	Pepper-bark tree	Yes
Zanthoxylum	*Capense*	(Thunb.) Harv. (Rutaceae)	Umlungumabele	Small knobwood	Yes
Ziziphus	*Mucronata*	Wild. (Rhamnaceae)	Umlahlankosi	Buffalo-thorn	Yes

biodiversity and conservation. This is due to the destructive nature of removing bark from the trunk or roots of medicinal species. Scholars continue to deliberate over the perceived threat to biodiversity and contest the necessity of using bark in favour of stems and leaves. Suggestions have also been made on how to preserve biodiversity without having an impact on the freedom of cultural practice (Kalaba et al. 2010; van Wyk and Prinsloo 2018; Wiersum et al. 2006). An understanding of the chemical uniqueness of bark compared to leaves may add essential information to this ongoing discussion. Unfortunately, studies that quantitatively explore the comparison between leaves and bark are scarce.

The harvesting of bark in preference to leaves or stems requires considerably greater manual labour, implicating that this practice is motivated by empirically determined superiority in therapy. In exploring this further, prospective chemical studies are undertaken, but they merely characterize chemical profiles, which is a limited approach in understanding the therapeutic attributes of the species. Thus, chemical studies are often complemented with bioassay data. Both approaches help to build the picture of the diversity of metabolites and the therapeutic potency of bark, reported in ethnobotanical studies.

A major criticism of ethnopharmacological studies is in relation to the feasibility that the bioactive metabolites are extracted by traditional methods. These metabolites may be significant to therapeutic applications, but the modality of use determines which metabolites are transferred from the bark to the person, either via ingestion, inhalation or contact with the dermis. For example, several bark therapies are used in smoke fumigation practice, driving a range of molecules onto skin surfaces, or into the lungs. Smoke fumigation promotes transfer of volatile organic compounds and other metabolites as aerosols, which increases the human dose of semi-volatile ingredients that are not regarded as essential oil components (Khumalo et al. 2019b; Sadgrove et al. 2014; Sadgrove and Jones 2014b).

Extraction of specialized metabolites into water for use in medicine is also common practice (Khumalo 2018). Extractions that are performed using water at room temperature result in preferential dissolution of polar metabolites, which may improve solubility of lipophilic ingredients, particularly when the biota is rich in surfactants, such as saponins or lecithins. The pH of the extract will also determine solubility of ionizable compounds, such as free carboxylic acids or alkaloids. Alternatively, extractions using boiled water may liquidate lipophilic ingredients, causing flocculants to form upon cooling. Thereafter, flocculants are ingested when the solution is drunk, entering the body as particles (nanoparticles) rather than as solutes. This phenomenon is familiar to traditional Chinese medicine, recently demonstrated by boiling liquorice to produce nanoparticles of proteins that encapsulate lipophilic ingredients (Zhou et al. 2019).

Comment on the comparison of leaves to bark

While there are limited studies that compare leaves to twigs, some examples were found. From the comparison of *Curtisia dentata* (Burm.f.) C.A.Sm., an apparent paradox was revealed. In an antimicrobial assay, extracts of leaves and twigs were more active against microorganisms than the extracts of the stem bark (Shai et al. 2009). The authors didn't isolate and

Table 2 Phytochemical data related to 63 of the species listed in Table 1

Species	Bark type	Chemistry
Albizia adianthifolia	Stem & root bark	Essential oils, β-caryophyllene, α-humulene, selin-11-en-4-α-ol, other sesquiterpenes (Akande et al. 2018)
Araucaria heterophylla	Resin from stem bark	Three labdane diterpenes, abda-8(17),14-diene, 13-epicupressic acid, and 13-O-acetyl-13-epicupressic. Essential oils, α-copaene (29.9%), germacrene D (21.4%), γ-gurjunene (9.7%), δ-cadinene (7.1%), and sandaracopimara-8(14),15-diene (6.5%) (Abdel-Sattar et al. 2009; Verma et al. 2014)
Balanites maughamii	Tree bark	Scopoletin and stigmasterol (Langlois 2000)
Berchemia discolor	Root bark	Putative new prenylated flavonoids and pterocarpans, plus the known analogues nitidulin, amorphigenin, and dabinol (Chin et al. 2006)
Bersama lucens	Tree & root bark	New and known triterpenes, such as lup-30-al-3b-ol and lup-20-(30)-en-3,29-diol-7-one (Koorbanally et al. 2008)
Bersama swinnyi	Tree & root bark	New and known triterpenes, such as 24-propylcholestan-7,15,20-triol (Koorbanally et al. 2008)
Bobgunnia madagascariensis	Tree bark	Triterpenes, lup-20(29)-en-3-one (Adeyemi and Amupitan 2011). Flavonoids, quercetin (Adeyemi et al. 2010)
Brackenridgea zanguebarica	Stem bark	Chalcone dimers, such as calodenin B, isochamaejasmine, and brackenin (Issa et al. 2013)
Bridelia micrantha	Stem bark	Phenols, trans-triacontyl-4-hydroxy-3-methoxycinnamate and catechin, triterpenes, friedelin and betulinic acid (Munayi 2016)
Calodendrum capense	Root bark	Sesquiterpene, calodendrolide, and the limonoids, limonin and limonin diosphenol (Kiprop et al. 2005). Alkaloids, capensenin and confusameline, furanocoumarins psolaren and bergapten (Okwemba et al. 2018)
Cassine papillosa	Stem bark	Peltogynoids, (+)-6R,13R-11,1 l-dimethyl-1,3,8,10-tetrahydroxy-9-methoxypeltogynan and (-))-4′-0-methoxyepigallocatechin, proanthocyanidins, galactitol, tingenone, and tingenin B, pentacyclic triterpenes, canophyllol, 3-hydroxyIupeol and 30-hydroxylup 20(29)-en-3-one (Drewes and Mashimbye 1993)
Cassipourea flanaganii	Stem bark	Diterpenes, ent-atis-16-en-19-al, ent-atis-16-en-19-oic acid, ent-atis-16-en-19-ol, ent-kaur-16-en-19-oic acid, ent-kaur-16-en-19-al, ent-manoyl oxide, amines, guinesine A, guinesine B, guinesine C, phenols, lichenxanthone, 2,4-dihydroxy-3,6-dimethyl benzoic acid methyl ester, docosyl ferulate, lynoside, triterpenes, lupeol, β-amyrin, sterols, stigmasterol, sitosterol and sitosterol-O-glucoside (Langat et al. 2021)
Cinnamomum camphora	Tree bark	Essential oils, D-camphor (51.3%), 1,8-cineole (4.3%), and α-terpineol (3.8%) (Guo et al. 2016). Phenols, hydroxy and methoxy benzoic acid derivatives (Shu et al. 2022)
Combretum caffrum	Stem bark	Phenols, combretastatin, 3,3′,4′-tri-O-methylellagic acid and acacetin (Pettit et al. 1987, 1995)
Commiphora africana	Stem bark	Resveratrol derivatives (phenols), (*E*)-resveratrol 3-O-rutinoside, 5-methoxy-(*E*)-resveratrol 3-O-rutinoside, pinostilbene, and 3-hydroxy-5-methoxybenzoic acid (Segun et al. 2019)
Croton gratissimus	Stem bark	Cembranolides, (+)-[1R*,2S*,7S*,8S*,12R*]-7,8-epoxy-2,12-cyclocembra-3E,10Z-dien-20,10-olide, among others (Mulholland et al. 2010)
Croton sylvaticus	Tree bark	Diterpenes, crotohalimaneic acid, 15-acetoxy-2-oxo-trans-ent-cleroda-3,13-diene, and hardwickiic acid among others. Triterpenes and sterols, lupeone, β-amaryn, and sitosterol, among others (Maroyi 2017)
Cryptocarya latifolia	Tree bark	α-Pyrone derivatives, 6-substituted-5,6-dihydro-α-pyrones and dioxabicyclo [3,3,1]nonan-2-one derivatives (Drewes et al. 1995b)
Dichrostachys cinerea	Root & tree bark	Meroterpenes in root bark, dichrostachines A−R (Long et al. 2009). Triterpenes and sterols in tree bark, friedelan-3-one, friedelan-3β-ol, betulinic acid, and 3-O-β-D-glucopyranosyl-β-sitosterol, fatty acid derivatives and flavonoids, apigenin, luteonin, and related derivatives (Fotie et al. 2004)
Dombeya rotundifolia	Stem bark	Sterols, lupeol and sitosterol (Ndwigah et al. 2005)

Table 2 continued

Species	Bark type	Chemistry
Ekebergia capensis	Tree & root bark	Tree bark, acyclic triterpenes, 2,3,22,23-tetrahydroxy-2,6,10,15,19,23-hexamethyl-6,10,14,18-tetracosatetraene and 2-hydroxymethyl-2,3,22,23-tetrahydroxy-6,10,15,19,23-pentamethyl-6,10,14,18-tetracosatetraene, plus known pentacyclic triterpenes (Nishiyama et al. 1996; Oyedeji-Amusa et al. 2021). Root bark, oleanonic acid, 3-epi-oleanolic acid, oleanolic acid, ekeberin A, 2-hydroxymethyl-2,3,22,23-tetrahydroxy-6,10,15,19,23-pentamethyl-6,10,14,18-tetracosatetraene, and 2,3,22,23-tetrahydroxy-2,6,10,15,19,23-hexamethyl-6,10,14,18-tetracosatetraene (Irungu et al. 2014)
Elaeodendron transvaalensis	Tree bark	Triterpenes and sterols, lup-20(29)-ene-30-hydroxy-3-one, 3,28-dihydroxylbetuli-20(29)-ene, 3-oxo-28-hydroxylbetuli-20(29)-ene, 6β-hydroxy-lup-20(29)-ene-3-one, β-sitosterol, Ψ-taraxastanonol and lup-20(30)-ene-3α,29-diol, flavonoid, 4'-O-methyl-epigallocatechin, canophyllol, canophyllal, a peltogynoid, (+)-11,11-dimethyl-1,3,8,10-tetrahydroxy-9-methoxypeltogynan (Drewes et al. 1991; Khumalo et al. 2019a; Maroyi and Semenya 2019; Tshikalange and Hussein 2010)
Entandrophragma caudatum	Tree & root bark	Limonoids and protolimonoids, phragmalin; phragmalin 3,30-diisobutyrate, phragmalin 3-isobutyrate-30-propionate, entandrophragmin B (12α-acetoxyphragmalin 3-nicotinate-30-isobutyrate), bussein A and B; entandrophragmin, 3α–turreanthin, and melianone (Ansell and Taylor 1988; Oyedeji-Amusa et al. 2021)
Eriocoelum microspermum	Root bark	Terpenoid glycosides, 3-O-α-L-rhamnopyranosyl-(1 → 3)-[α-L-rhamnopyranosyl-(1 → 2)]-α-L-arabinopyranosylhederagenin, 3-O-α-L-rhamnopyranosyl-(1 → 3)-[β-D-glucopyranosyl-(1 → 3)-α-L-rhamnopyranosyl-(1 → 2)]-α-L-arabinopyranosylhederagenin, 3-O-α-L-rhamnopyranosyl-(1 → 3)-[β-D-xylopyranosyl-(1 → 3)-α-L-rhamnopyranosyl-(1 → 2)]-α-L-arabinopyranosylhederagenin, 3-O-α-L-rhamnopyranosyl-(1 → 4)-[α-L-rhamnopyranosyl-(1 → 2)]-α-L-arabinopyranosylhederagenin 28-O-β-D-glucopyranosyl ester, 3-O-α-L-rhamnopyranosyl-(1 → 3)-β-D-xylopyranosyl-(1 → 4)-β-D-xylopyranosyl-(1 → 3)-α-L-rhamnopyranosyl-(1 → 2)-α-L-arabinopyranosylhederagenin, 3-O-α-L-rhamnopyranosyl-(1 → 3)-α-L-arabinopyranosyl-(1 → 4)-β-D-xylopyranosyl-(1 → 3)-α-L-rhamnopyranosyl-(1 → 2)-α-L-arabinopyranosylhederagenin, 3-O-β-D-xylopyranosyl-(1 → 4)-α-L-arabinopyranosyl-(1 → 4)-β-D-glucopyranosyl-(1 → 3)-α-L-rhamnopyranosyl-(1 → 2)-α-L-arabinopyranosylhederagenin, 3-O-α-L-rhamnopyranosyl-(1 → 4)-α-L-rhamnopyranosyl-(1 → 3)-α-L-arabinopyranosyl-(1 → 4)-β-D-glucopyranosyl-(1 → 3)-α-L-rhamnopyranosyl-(1 → 2)]-α-L-arabinopyranosylhederagenin, 1-O-[β-D-xylopyranosyl-(1 → 3)-[α-L-rhamnopyranosyl-(1 → 2)]-β-D-glucopyranosyl-(1 → 4)-α-L-rhamnopyranosyl-(1 → 6)]-[β-D-xylopyranosyl-(1 → 3)]-[α-L-rhamnopyranosyl-(1 → 2)]-β-D-glucopyranosyl-(2E,6E)-farnes-1-ol, 1-O-[β-D-glucopyranosyl-(1 → 3)-[α-L-rhamnopyranosyl-(1 → 2)]-β-D-glucopyranosyl-(1 → 4)-α-L-rhamnopyranosyl-(1 → 6)]-[β-D-xylopyranosyl-(1 → 3)]-[α-L-rhamnopyranosyl-(1 → 2)]-β-D-glucopyranosyl-(2E,6E)-farnes-1-ol (Pertuit et al. 2018a)
Erythrina lysistemon	Tree bark	Prenylated isoflavones and pterocarpans, erybraedin A, phaseollidin, abyssinone V-4′ methyl ether, eryzerin C, alpumisoflavone, cristacarpin and lysisteisoflavone (Sadgrove et al. 2020a)
Eucalyptus sideroxylon	Tree bark	Flavonoids, quercetin-O-dihexoside, engeletin (dihydrokaempferol rhamnoside), engeletin isomers, naringenin and sideroxylin. Ellagic acid, related derivative such methyl ellagic, dimethyl ellagic, and trimethyl ellagic acids. Triterpenes, such as trihydroxy oleanenoic (arjunolic) acid, O-p coumaroyl pentacyclic triterpene, oleanolic, ursolic, morolic acid, eucalyptanoic acid, methyl morolate 1, β-sitosterol 2, phenols, syringaldeyhde, and 7′-Deoxyguajavadial A (Ashour et al. 2019)
Euclea natalensis	Stem bark	Phenol, shinanolone, phenol dimer, octahydroeuclein and triterpenes, 20(29)-lupene-3β-isoferulate, lupeol, and botulin (Weigenand et al. 2004)
Ficus glumosa	Stem bark	Ceramides, (2R,7E)-2-hydroxy-N-[(2S,3S,4R)-1,3,4-trihydroxyhexadecan-2-yl]hexacos-7-enamide and (2R)-N-[(2S,3S,4R,9Z)-1-O-[(β-D-glucopyranosyl]-3,4-dihydroxyheptadec-9-en-2-yl]-2-hydroxypentacosanamide (Nana et al. 2012)
Garcinia gerrardii	Stem bark	Xanthones, such as xanthone, garcigerrin A, and B (Sordat-Diserens et al. 1989)

Table 2 continued

Species	Bark type	Chemistry
Garcinia livingstonei	Root bark	Prenylated and dimeric xanthones, 1,4,5-trihydroxy-3-(3-methylbut-2-enyl)-9H-xanthen-9-one, garcilivin A, B & C, 12β-hydroxy-des-D-garcigerrin A. A biflavanoid, ent-naringeninyl-(I-3α,II-8)-4′-O-methylnaringenin (Mbwambo et al. 2006; Sordat-Diserens et al. 1992a, 1992b)
Haplocoelum congolanum	Root bark	Triterpenoid saponins, 3-O-(4-O-[3-hydroxy-3-methylglutaryl])-α-l-arabinopyranosyl-(1 → 3)-α-l-rhamnopyranosyl-(1 → 2)-[β-d-glucopyranosyl-(1 → 4)]-α-l-arabinopyranosyloleanolic acid and 3-O-α-l-arabinofuranosyl-(1 → 3)-α-l-rhamnopyranosyl-(1 → 2)-[β-d-glucopyranosyl-(1 → 4)]-α-l-arabinopyranosyloleanolic acid (Pertuit et al. 2019)
Harpephyllum caffrum	Stem bark	Phenols, cardanols, an alkyl p-coumaric acid ester, and (+)-catechin (Moodley et al. 2014)
Kigelia africana	Stem & root bark	Stem bark: Napthaquinones, kigelinone, isopinnatal, and 2-(-hydroxyethyl)naphtho[2,3-b]furan-4,9-dione. Root bark: Napthaquinones: Isopinnatal, kigelinol, isokigelinol, 2-(1-hydroxyethyl)-naphtho[2,3-b]furan-4,9-quinone, isopinnatal, kigelinol, and isokigelinol (Gupta and Jain 2019)
Lannea schweinfurthii	Root bark	3-((*E*)-nonadec-16′-enyl)phenol, 1-((*E*)-heptadec-14′-enyl)cyclohex-4-ene-1,3-diol, catechin, and 1-((*E*)-pentadec-12′-enyl)cyclohex-4-ene-1,3-diol (Yaouba et al. 2018)
Macaranga capensis	Tree bark	Triterpenes, 3α-hydroxyaleuritolic acid 2-p-hydroxybenzoate and 3-acetoxyoleanolic acid (Majeed 2020)
Maytenus undata	Stem bark	Triterpenes, oleanolic acid, β-sitosterol, 3-oxo-28-friedelanoic acid, β-amyrin, lupeol and lupenone (Muthaura et al. 2017)
Ochna holstii	Stem bark	Flavonoids and chalconoids, ouratein D, isochamaejasmin A, 7′,7″-di-O-methylisochamaejasmin, campylospermone A, liquiritigeninyl-(1–3,II-3)-naringenin, isoliquitigenin, terminalionone, flavumchalcone, lophirone F, 2,3-dihydrocalodenin B, holstiinone A, holstiinone B, holstiichalcone I, holstiichalcone II, holstiichalcone III, and calodenin B (Kalenga et al. 2021)
Ocotea bullata	Stem bark	Neolignans, ocobullenone, iso-ocobullenone, a neolignan ketone (Drewes et al. 1995a) and a diastereomer (Zschocke et al. 2000)
Olax obtusifolia	Root bark	Triterpenoid saponins, 3-O-α-l-rhamnopyranosyl-(1 → 4)-α-l-rhamnopyranosyl-(1 → 3)-β-d-glucuronopyranosyloleanolic acid, 3-O-α-l-rhamnopyranosyl-(1 → 4)-α-l-rhamnopyranosyl-(1 → 3)-β-d-glucuronopyranosyloleanolic acid 28-O-β-d-glucopyranosyl ester, 3-O-α-l-rhamnopyranosyl-(1 → 3)-β-d-glucopyranosyl-(1 → 2)-[β-d-glucopyranosyl-(1 → 3)]-β-d-glucuronopyranosyloleanolic acid and 3-O-α-l-rhamnopyranosyl-(1 → 3)-β-d-glucopyranosyl-(1 → 2)-[β-d-glucopyranosyl-(1 → 3)]-β-d-glucuronopyranosyloleanolic acid 28-O-β-d-glucopyranosyl ester (Pertuit et al. 2018b)
Peltophorum africanum	Tree bark	Formyl phloroglucinols, 1-O-(E)-p-coumaroylbergenin, bergenin and norbergenin (Mebe and Makuhunga 1992). Flavonoids and phenolics but details of plant organ are scanty (Mazimba 2014)
Piptadeniastrum africanum	Stem bark	Triterpenoid saponins, piptadeniaoside, 3-O-β-[α-L-arabinopyranosyl-(1 → 2)-α-L-arabinopyranosyl-(1 → 3)-β-D-glucopyranosyl]maslinic acid-28-[β-D-glucopyranosyl-(1 → 2)-α-L-rhamnopyranosyl] ester, and 3-O-β-[α-L-arabinopyranosyl-(1 → 2)-α-L-arabinopyranosyl-(1 → 3)-β-D-glucopyranosyl]maslinic acid-28-[β-D-glucopyranosyl-(1 → 6)-β-D-glucopyranosyl-(1 → 2)-α-L-rhamnopyranosyl] ester (Noté et al. 2013)
Protorhus longifolia	Stem bark	Triterpenes, 3-oxo-5α-lanosta-8,24-dien-21-oic acid, 3β- hydroxylanosta-9,24-dien-24-oic acid, and methyl-3β-hydroxylanosta-9,24-dienoate (Mosa et al. 2014, 2011)
Prunus africana	Tree bark	Fatty acids, myristic acid, palmitic acid, linoleic acid, lignoceric acid, behenic acid, and oleic acid. Sterols and triterpenes, ursolic acid and sitosterol (Hass et al. 1999)
Ptaeroxylon obliquum	Tree bark	Aromadendrane diterpene, cneorubin X (prenylated sesquiterpene) (Mulholland and Mahomed 2000)
Pterocarpus angolensis	Tree bark	Epicatechin derivatives, [(-)-epicatechin, epicatechin-3-O-galate, epicatechin (4β–8)-epicatechin (B2), and a hexamer of epicatechin (Samie et al. 2009)

Table 2 continued

Species	Bark type	Chemistry
Rauvolfia caffra	Stem bark	Indole alkaloids, such as ajmaline, norajmaline (dihydroindoles), ajmalicinine, ajmalicine (heteroyohimbines), geissoschizol (*E*-seco indole), pleiocarpamine (Nasser and Court 1984) raucaffricine, N-methylsarpagine, spegatrine (Tlhapi et al. 2019) rauvolfianoids A and B (Bitombo et al. 2022)
Sclerocarya birrea	Tree bark	Phenols, digalloylated procyanidin B, epicatechin 3-O-gallate and related derivatives (Russo et al. 2013)
Securidaca longepedunculata	Tree & root bark	Tree bark: Phenols, β-D-(3,4-disinapoyl)fructofuranosyl-α-D-(6-sinapoyl)glucopyranoside, β-D-(3-sinapoyl)fructofuranosyl-α-D-(6-sinapoyl)glucopyranoside, sinapoic acid, caffeic acid, 4,5-dicaffeoyl-D-quinic acid, and 3,4,5-tricaffeoyl-D-quinic acid (De Tommasi et al. 1993). Root bark: methyl salicylate (Alitonou et al. 2012), 3-hydroxybenzoic acid, 3-hydroxy-4-methoxybenzoic acid, and 3,4-dimethoxy-7-hydroxyxanthone (Tiksa et al. 2019)
Securidaca welwitschia	Stem bark	Presenegenin glycosides, 3-O-(β-D-glucopyranosyl)presenegenin 28-[O-β-D-xylopyranosyl-(1 → 4)-O-α-L-rhamnopyranosyl-(1 → 2)-O-[β-D-glucopyranosyl-(1 → 3)]-4-O-[(E)-3,4-dimethoxycinnamoyl]-β-D-fucopyranosyl] ester, 2,3-O-(β-D-glucopyranosyl)presenegenin 28-[O-β-D-galactopyranosyl-(1 → 4)-O-β-D-xylopyranosyl-(1 → 4)-O-3-O-acetyl-α-L-rhamnopyranosyl-(1 → 2)-O-[β-D-glucopyranosyl-(1 → 3)]-4-O-[(E)-3,4-dimethoxycinnamoyl]-β-D-fucopyranosyl] ester and presenegenin (Timité et al. 2010)
Sideroxylon inerme	Stem bark	Epigallocatechin gallate and procyanidin B1 (Momtaz et al. 2008)
Spirostachys africana	Stem bark	Triterpenes, D-friedoolean-14-en-oic acid (3-acetyl aleuritolic acid), lupeol, diterpenes, ent-2,6α-dihydroxy-norbeyer-1,4,15-trien-3-one (diosphenol 2) and ent-3β-hydroxy-beyer-15-ene-2-one (Mathabe et al. 2008)
Strychnos henningsii	Stem & root bark	Alkaloids, holstiine, splendoline, 23-hydroxyspermostrychnine, 19-epi-23-hydroxyspermostrychnine, retuline, henningsiine, deshydroxyacetylhenningsiine, O-acetylhenningsiine, 3-hydroxyhenningsiine, henningsiine-N(4)-oxide, 23-hydroxyspermostrychnine-N(4)-oxide, 17,23-dihydroxyspermostrychnine, spermostrychnine, henningsamide, O-acetylhenningsamide, deshydroxyacetylhenningsamide and cyclostrychnine (Massiot et al. 1991)
Syzygium cordatum	Tree bark	Anthocyanins, leucodelphinidin and leucocyanidin, triterpenes, friedelin, epi-friedelinol, β-sitosterol, arjunolic acid, phenols, gallic acid, ellagic acid hexahydroxydiphenic acid, and a gallic acid-ellagic acid heterodimer (Candy et al. 1968; Maroyi 2018)
Terminalia catappa	Stem bark	Phenol, 3,4,5-trimethoxyphenyl-1-O-(4-sulfo)-β-D-glucopyranoside, and triterpene saponins, chebuloside II, arjunoglucoside II, triterpenes, arjunolic acid and 3-betulinic acid, and the sterol, sitosterol-3-O-β-D-glucopyranoside (Pertuit et al. 2015)
Terminalia sericea	Root bark	Triterpenes and sterols, sericic acid, sericoside (Mbunde et al. 2021), β-sitosterol, β-sitosterol-3-acetate, lupeol and stigmasterol-3-one, phenols, epicatechin, catechin, and epigallocatechingallocatechin (Nkobole 2011)
Terminalia superba	Stem bark	Pentacyclic triterpenes, 2α,3β-dihydroxyolean-12-en-28-oic acid 28-O-β-D-glucopyranoside, 2α,3β, 21β-trihydroxyolean-12-en-28-oic acid 28-O-β-D-glucopyranoside, 2α,3β, 29-trihydroxyolean-12-en-28-oic acid 28-O-β-D-glucopyranoside, 2α,3β,23,27-tetrahydroxyolean-12-en-28-oic acid 28-O-β-D-glucopyranoside, and 2α,3β,23-trihydroxyolean-12-en-28-oic acid (Pertuit et al. 2015)
Tetrapleura tetraptera	Stem bark	Oleanane-type saponins, tetrapterosides A and B (Noté et al. 2009)
Turraea floribunda	Stem bark	Liminoid, floribundin F (1α,7α-12α -triacetoxy-4α -carbomethoxy-11β-(2-methylpropanoyloxy)-14β,15β-epoxyhavanensin) (Oyedeji-Amusa et al. 2021)
Vachellia xanthophloea	Tree bark	Hydrolysable tannins, gallic acid, tannic acid, catechin, catechol, m-hydroxy benzoic acid (Duraisamy et al. 2020)

Table 2 continued

Species	Bark type	Chemistry
Voacanga thouarsii	Tree bark	Alkaloids, voacangine, ibogaine, voacamine, vobtusine, voacristine, iboluteine, vobasine, 18′-decarbomethoxyvoacamine and voaluteine (Goldblatt et al. 1970)
Warburgia salutaris	Stem & tree bark	Drimane sesquiterpenes, drimenol, 12α-acetal-polygodial, polygodial, ugandensidial, and warburganal, linear sesquiterpene, *E*-nerolidol (Khumalo et al. 2019b)
Zanthoxylum capense	Stem bark & knobs	The amide, pellitorine, the lignan xanthoxylol-γ,γ-dimethylallyl ether, and the sterol sitosterol-β-D-glucoside (Steyn et al. 1998). Alkaloids, chelerythrine, 6-hydroxydihydrochelerythrine, and rutaecarpine. Phenols, dodecyl-trans-p-coumarate, a lignan, sesamin, a flavanol, catechin, triterpenes, lupeol and sitosterol, pigments (possibly only in leaves), pheophytin a and lutein (Bodede et al. 2017)
Ziziphus mucronata	Root bark	Cyclopeptide alkaloids, mucronine J (Auvin et al. 1996), and derivatives (Barboni et al. 1994)

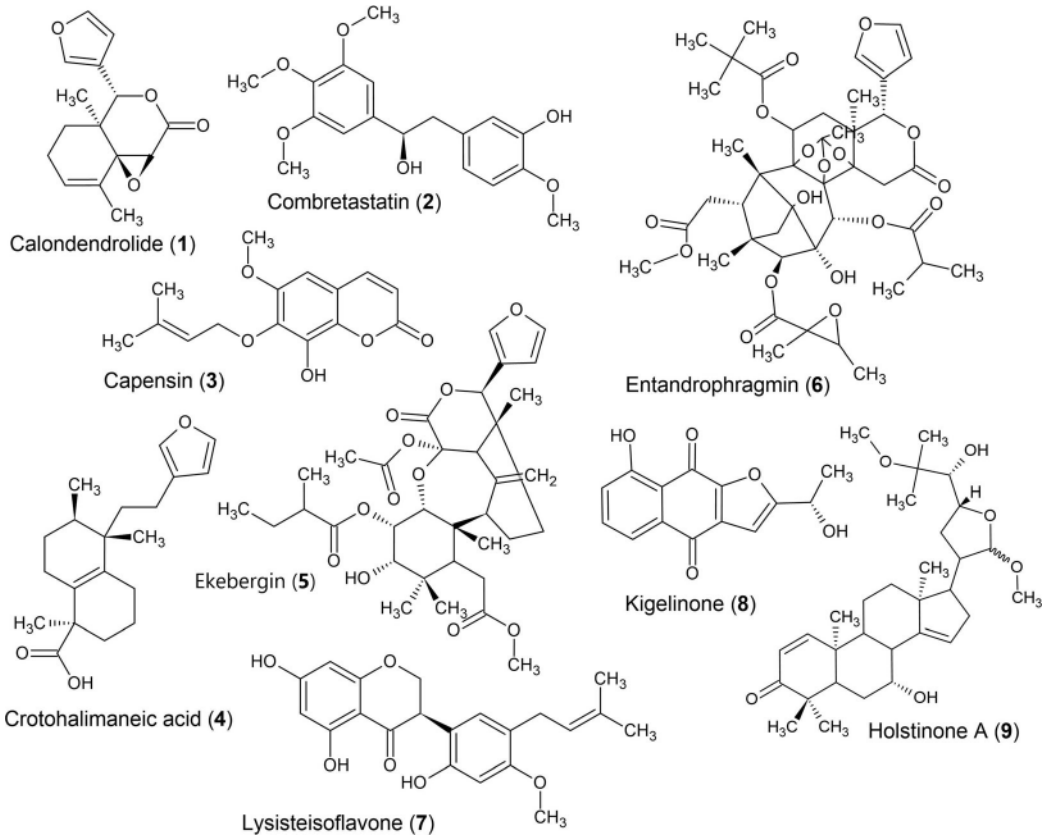

Fig. 1 Structures 1–9, illustrating the range of compounds isolated from medicinal barks in southern Africa

identify the antimicrobial compounds, but used thin layer chromatography to determine that the lipophilic fraction of the three organs was chemically similar. In another study, pentacyclic triterpenes were identified in leaves, including lupeol, betulinic acid, ursolic acid and 2α-hydroxyursolic acid (Shai et al. 2008). The latter two are potently active against various

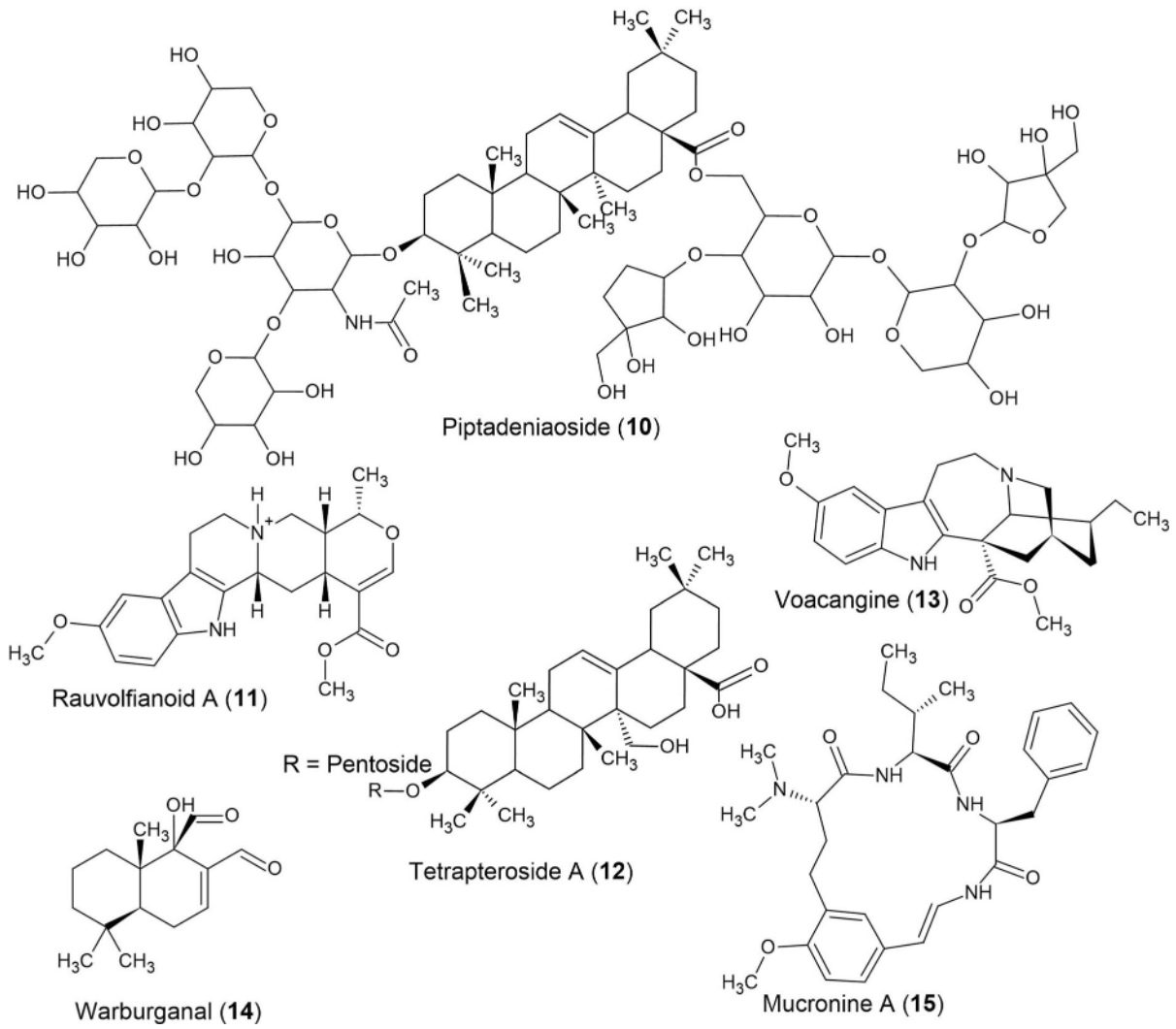

Fig. 2 Structures 10–15, illustrating the range of compounds isolated from medicinal barks in southern Africa

microorganisms (Jesus et al. 2015) and probably explain the antimicrobial activity observed.

The above example does not conclusively prove that leaves are more useful in anti-infective applications, because an artefact of the scientific method may obscure other factors. Without further interpretation, it conveys that the antimicrobial compounds are more abundant in leaves. However, another possibility is that a higher yield of other metabolites in bark diluted the active ingredients in the respective extract, i.e., while the authors did not report extract yields, if a tenfold greater mass was extracted from bark compared to leaves, with only a fivefold reduction in antimicrobial potency, then the pre-extracted bark is more potent than the pre-extracted leaves. This possibility should be considered in moving forward, to understand why the bark is chosen for anti-infective applications by herbalists.

In another example of a species from the genus *Strychnos* (*S. henningsii* Gilg) the diveristy of alkaloids in the leaves was higher compared to the bark. While the same bark alkaloids were identified in leaves, another 13 were assigned in leaves, including cyclostrychine, an alkaloid that is similar to the highly toxic alkaloid strychnine (Massiot et al. 1991). The implication is that the choice of bark in preference to leaves in medicinal practice is a matter of safety, rather than potency.

In a similar study of *Elaeodendron croceum* (Thunb.) DC., it was revealed that most compounds in the leaves are very toxic, containing the toxic substances 20-hydroxy-20-epi-tingenone, tingenone, and tingenine B, and the non-toxic substances 11α-hydroxy-β-amyrin and naringenin (Yelani et al. 2010). Unfortunately, no studies were found on the bark of this species, but the comparison of leaves to bark is necessary to understand this further.

A toxicity study of *Ekebergia capensis* Sparrm against carcinoma cell lines and vero (normal) cells demonstrated that root bark extracts were substantially more toxic than leaves, and toxicity was relatively uniform between cancerous and normal mammalian cells (Irungu et al. 2014). Despite this, most of the EC50 values reported were relatively high to be considered replicable in vivo, due to pharmacokinetic factors (Sadgrove and Jones 2019). The chemical analysis revealed that the two organs were completely different at the level of chemical class, with triterpenes dominating in the root bark compared to a limonoid and several flavonoid glycosides in the leaves. Ethnobotanical reports convey that all plant parts are used in traditional medicine, either internally or topically for various applications to achieve anti-infective, anti-cancerous and cardiovascular effects (Oyedeji-Amusa et al. 2021). Thus far, the mechanisms are not explained by the in vitro data (Sadgrove and Jones 2019), and the toxicity studies need to be interpreted in the context of pharmacokinetics and pharmacodynamics.

In a final example, a comparison of the major compounds in the leaves and bark of *Croton gratissimus* Burch (Langat et al. 2011; Mulholland et al. 2010), demonstrated a greater diversity of cembranolides in the leaves (16 isolates, compared to 4 in bark). While the two plant organs shared a common biosynthetic group, being the the cembranolides, there was minimal overlap of chemical identities.

In the context of therapeutic attributes of this species, there may be a geographical component controlling local use or efficacy. This is because another study on the chemistry of *C. gratissimus* revealed that specimens growing in other parts of the country are dominated by abietane and halimane dieterpenes (Sadgrove et al. 2019), and do not contain the cembranolides described for the specimen cultivated in Durban of coastal South Africa. In this regard, geographical specificity, plasticity of metabolite expression (chemophenetics) (Ramos et al. 2023), and chemotypes (Sadgrove 2020) should be considered when interpreting chemical data of any African species.

Comment on metabolites as indicators of therapeutic value: pharmacokinetics

The vast majority of chemical studies found in the literature did not follow up with bioassays. Where bioassay data was found, scholars predominantly focus on anti-infective activity, or cytotoxicity against cancer cell lines. Unfortuantely, routine bioassays are limited in their ability to explain therapeutic mechanisms of medicinal species. Many of the bioassays were developed to guide the synthesis of drugs as selective targets of isolated biochemical processes, but for natural products it would be too much of a coincidence if their mechanisms are via the same singular biochemical process. More importantly, pharmacokinetic processes in the body drastically change natural product extracts; it is difficult to ascertain which of the xenobiotic intermediates play a role in the therapeutic results (Sadgrove and Jones 2019).

The medicinal bark species of southern Africa are predominantly anti-infective, i.e., they are antimicrobial against select pathogens or a broad spectrum of pathogens that are Gram-positive, Gram-negative, a fungi or yeast. Antimicrobial assays of bark extracts made in a laboratory are therefore translatable to topical applications where direct contact between the bark extracts and microorganisms is feasible. For example, placing extrats directly onto a skin infection, wound, rash or fungal infection will conceivably reproduce the in vitro data. It is also feasible where targetted pathogens are in the gastrointestinal space, because concoctions and decoctions carry metabolites directly to the pathogens in the alimentary canal. In a final example, anti-infective compounds that are either volatile or semi-volatile, are easily transferred to the lungs by smoke fumigation, achieving direct contact with respiratory pathogens (Khumalo et al. 2019b).

However, medicinal bark extracts that are taken to target infections via the systemic passage (portal circulation, metabolism and elimination) require expert interpretation, particularly where in vitro studies are performed without consideration to pharmacokinetic viability (Sadgrove and Jones 2019). Not

only do digestive processes alter the metabolites, but gut microbes catabolize them. Another factor to determine translation is the transdermal transport of specific metabolites across the intestinal wall into portal circulation, or the exclusion and elemination of others.

For example, where saponins are present in medicinal bark species, the pharmacokinetic interpretation becomes more complex. Saponins are known to soothe skin and topical autoimmune-related inflammatory afflictions (Passos et al. 2022), which may enact therapeutic effects to the intestinal epidermis. But ingested saponins are not absorbed through the intestinal wall into portal circulation, rather, the sugars are hydrolyzed in the digestive process and a simpler triterpene conjugates, or triterpene aglycones, are absorbed. These triterpenes tend to enact the same anti-inflammatory effects as the more complex saponin, after binding to blood albumin and being transported to various sites in the human body (Sadgrove and Jones 2019).

One exception to the poor dermal penetration ability of saponins is the highly complex structures that are aminated. An example is the group of saponins known as the avicins, which have a geranly moiety and an acetamide group. These types of saponins travel across dermal layers as efficiently as moderately lipophilic molecules (Pino et al. 2014), which appears to be a glaring contradiction to pharmacokinetic theory, but constitutes an exception to the rule. Not surprisingly, the bark of one southern African species, *Piptadeniastrum africanum* (Hook.f.) Brenan., contains acetamide saponins, known as the piptadeniaosides (Fig. 2) (Noté et al. 2013). Currently there is no research examining transdermal potential of these saponins, but it is a worthy future endeavour.

Another pharmacokinetic issue related to bioassay data is the concentration reported for in vitro studies, which are commonly reported for antimicrobial effects or inhibition of cancer cells. It is common for reported concentrations to far exceed maximum concentrations achieved in human plasma, due to the rate of conjugation and elimination in metabolism. Such concentrations are generally above 10 μg mL^{-1}. While some natural products can reach concentrations as high as 5 μg mL^{-1}, most natural products will only achieve systemic concentrations of up to 1 μg mL^{-1}.

Nevertheless, some of the bioassay data found in the course of this review is indeed of interest, where low values of 1–5 μg mL^{-1} were reported. Examples of bioactivity studies and their outcomes include the antioxidant activity of phenolics in bark of *P. africaanum* (Mazimba 2014), anti-cancerous effect of trans-triacontyl-4-hydroxy-3-methoxycinnamate from *B. micrantha* (Munayi 2016), the anti-cancerous effect of pellitorine (Ee et al. 2010) assigned in bark of *Z. capense* (Steyn et al. 1998), or the anti-inflammatory effects of sibyllenone, a meroterpene from *O. bullata* (Zschocke et al. 2000).

As mentioned above, there are also various studies that report bioassay data requiring further interpretation, or even dismissal. But this does not nullify the therapeutic attributes of species, it merely fails to explain them. In many cases, the phytochemical diversity of orally ingested nutraceutical items may be considered prophylactic for numerous diseases (Sadgrove 2022; Sadgrove and Simmonds 2022), by facilitating a return to homeostasis in cells (i.e., restore redox balance). For example, species that are rich in flavonoids may be regarded as facilitating a recovery to the redox balance of cells in stressed tissues (Crown et al. 2019), either by stimulating the expression of endogenous antioxidants (glutathione, superoxide dismutase or catalase) (Kameoka et al. 1999) or by participating at complex 1 of the electron transport chain, producing heterodimers referred to as 'spent antioxidants' (Huvaere et al. 2012). Such effects can be behind reducing the symptoms of disease, improving diabetes, and strengthening the immune system, supporting the body's resistance and recovery from infections.

Various studies that describe effects such as anti-inflammatory, anti-infectious or anti-cancerous activity, but report EC50 or MIC values that are not reached in human blood plasma (due to pharmacokinetic obstacles), may still be of relevance due to the accumulation of lipophilic ingredients in inflammed tissues. This is due to the metabolic process in the liver that generates glucuronide conjugates of natural products entering portal circulation from the digestive tract. Although glucuronides are conjugates that are made more polar to enable elimination via the kidneys, they will be deconjugated when in contact with any of the β-glucuronidase isozymes. β-Glucuronidases are expressed when macrophages and neutrophils are stimulated (Kawai 2014; Shimoi and Nakayama 2005), which is relevant to the modulation of inflammation by the body's conjugated androgens (Bianchi

2019). Thus, when natural product glucuronide conjugates enter tissues that are inflammed, such as infections or cancers, the removal of the glucuronic acid moiety decreases the plasma solubility of the compound, causing it to accumulate on-site to concentrations exceeding the safe levels in plasma and enacting biological affects, such as anti-infection, anti-cancer or anti-inflammation. Thus, some of the bioligcal effects ascribed to natural products in medicinal bark species may be considered relevant, but nevertheless, requiring further research.

In a final example, hydrolyzable and condensed tannins are ubiquitous in medicinal bark species. They are so common that they are frequently ignored in chemical studies and not reported. Tannins are generally determined as mixtures of hydrolysable and condensed forms. The two most common types of hydrolyzable tannin are ellagitannin and gallotannin. Ellagitannins are the most diverse and common group of hydrolyzable tannin, found for example, in the Myrtales (Yoshida et al. 2010), in some fruits (Barbara and Janja 2021), in the bark of most species in the genus *Eucalyptus* (Cadahía et al. 1997), and in multiple species from Nigeria (Ucella-Filho et al. 2022).

Ellagitannins are sugar conjugates of ellagic acid. They are instantly hydrolyzed in the acid conditions of the human stomach, converting to a mixture of sugars and ellagic acid. While some of the ellagic acid is abosrbed into portal circulation of the human body, a large portion is catabolized by gut microbiota, producing urolithin isomers, such as urolithin A, urolithin B, isourolithin, or any of the 10 others that are so far known (García-Villalba et al. 2022). The most common catabolites are urolithin A or B. Their presence/absence or ratio is determined by the nature of species in the gut microbiome, and potentially other factors, creating the supposed "urolithin phenotypes" that have been identified in studies (Tomás-Barberán et al. 2014).

A role for the therapeutic effects of urolithins and their potential as prophylactic agents against lifestyle disease, has been explored in the literature. When urolithins are produced from ellagic acid in the microbiome, they cross into portal circulation and circulate in the human system as either their free form, or as a conjugate produced in liver metabolism, with a urolithin glucuronide being the most common. Out of the 35 studies reviewed by Garcia-Villalba et al. (2022) it was concluded that they are not only prophylactic against cardiovascular disease, but they confer systemic anti-inflammatory effects, they are neuroprotectice, and may decrease risk of cancers. Thus, the efficacy of bark medicines that are ingested goes beyond what is conveyed in routine bioassays of crude extracts produced in the lab, due to pharmacokinetic processes occuring in the human body.

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