Revista Brasileira de Farmacognosia
https://doi.org/10.1007/s43450-024-00546-3

REVIEW

# Antineoplastic Activity of Selected Cytotoxic Plants from the Kalahari

**Divan Vogel**[1] · **Chrisna Gouws**[1] · **Frank van der Kooy**[1]

Received: 19 November 2023 / Accepted: 26 March 2024


**Abstract**
Plants are known to produce cytotoxic compounds, some of which are currently being used as chemotherapeutic agents for the treatment of cancer. With southern Africa's rich biodiversity, it could be worthwhile to study indigenous herbal medicine to discover more effective and safe cancer treatments as complementary and alternative therapies. From Africa, several plant species have been used by traditional therapists for the treatment of cancer with well-known examples including *Lessertia frutescens* (L.) Goldblatt & J.C.Manning (syn. *Sutherlandia frutescence* (L.) W:T.Aiton), Fabaceae, *Catharanthus roseus* (L.) G.Don, Apocynaceae, and *Tulbaghia violacea* Harv., Amaryllidaceae. Recently, *Artemisia afra* Jacq., Asteraceae, has also been shown to exhibit strong *in vitro* antineoplastic activity. This review focuses on *A. afra* and some lesser studied southern African plants from the Kalahari region. This selection was made based on field observations, traditional use, and literature summarizing recent developments and their potential as anticancer agents. *Ammocharis coranica* Herb., Amaryllidaceae, *A. afra*, *Dipcadi glaucum* (Burch. ex Ker Gawl.) Baker, Asparagaceae, *Elephantorrhiza elephantina* (Burch.) Skeels, Fabaceae, *Geigeria ornativa* O.Hoffm., Asteraceae, *Neltuma juliflora* (Sw.) Raf. (syn. *Prosopis juliflora* (Sw.) DC.), Fabaceae, and *Senna italica* Mill., Fabaceae, can be found in the Kalahari region stretching across three countries. Databases were consulted (Science Direct, Web of Science, Scopus, PubMed, and Google Scholar) and textbooks to collate scientific literature on the selected species. Lycorine seems to be the most promising bioactive compound isolated from *A. coranica* with *in vitro* cytotoxicity of 0.21 µg/ml ($IC_{50}$). Methanol extracts of *N. juliflora* appear to be highly active, while butanolic extracts are cytotoxic at a low concentration of 5.17 µg/ml against MCF-7. Isoalantolactone identified in *A. afra* also expressed good activity, being cytotoxic at a low concentration of 1.89 µg/ml. Tea infusions of *A. afra* were found to be cytotoxic at 6.0 µg/ml with a selectivity index of 10. Identification of active constituents, more in-depth *ex vivo/in situ* experiments, and eventually clinical trials should be conducted on the most promising plant extracts and/or compounds identified therein.

**Keywords** Antineoplastic · Cancer · Cytotoxicity · Medicinal plants · Phytochemicals · Traditional African medicine

## Introduction

The underlying cause of cancer is the abnormal growth and proliferation of any cell in the body. Because any cell type can cause cancer, literally hundreds of distinct types and sub-types of cancer are known. There is however a clear distinction between benign and malignant cell proliferation or tumors. A benign tumor is limited to its original position and can therefore usually be removed surgically whereas a malignant tumor is able to invade neighboring tissue and has the ability to spread, or metastasize, throughout the body via the circulatory systems. The latter is referred to as cancers, and it is their ability to invade and metastasize that makes cancer such a dangerous disease.

The cell type from which cancer originates dictates the name of the cancer and mainly falls into three categories, namely, carcinomas, leukemias/lymphomas, and sarcomas. Roughly 90% of cancers fall within the carcinoma category and are caused by malignancies of epithelial cells. Leukemias and lymphomas, which only account for approximately 8% of human cancers, develop from the blood-forming cells and cells of the immune system, respectively. Sarcomas, which are quite rare in humans, are solid tumors of connective tissues, such as muscle, bone, cartilage, and fibrous tissue. The tissues where cancer originates such as colon or prostate carcinomas are also used to further classify cancers,

✉ Frank van der Kooy
frank.vanderkooy@nwu.ac.za

[1] PharmacenTM, Centre of Excellence for Pharmaceutical Sciences, North-West University, Private Bag X6001, Potchefstroom 2520, South Africa

Published online: 15 April 2024

for example, melanoma which arises from the skin cell type melanocytes (Cooper 2000). Cancer is listed as one of the top ten causes of deaths globally and is one of the fastest-growing non-communicable diseases (Raimi et al. 2020).

Chemotherapeutic agents for the treatment of cancer are commonly derived from natural resources with roughly 60% of currently available drugs originating from terrestrial plants (Fouche et al. 2006). Current chemotherapeutic treatments are often accompanied by severe side effects and are too expensive to be accessible for most patients in developing countries (Raimi et al. 2020). Even more troublesome, the extensive use of chemotherapeutics has reached a therapeutic plateau (Zugazagoitia et al. 2016) and the occurrence of multi-drug resistant cancer (intrinsic as well as acquired) is increasing (O'Connor 2007). A similar approach currently being used for treating human immunodeficiency virus (HIV), malaria, and tuberculosis, where a combination of drugs is used, could be the best way to move forward (Zugazagoitia et al. 2016). Therefore, new treatments are urgently needed that are more effective, display fewer side effects, and can slow the emergence of drug resistance.

Between 1946 and 1980, 53.3% (40 of 75 small molecules) of all new chemical entities (NCEs) intended for therapeutic use in humans were of natural origin. From 1981 to 2019, 64.9% of new cancer drugs were of natural origin. Anti-infectives also showed a similar trend and indicate the importance of natural products in the discovery and development pipeline (Newman and Cragg 2020). Artemether (an artemisinin derivative from *Artemisia annua* L., Asteraceae) is one such drug and is used in combination with other drugs, for the treatment of severe quinine-resistant malaria (Afolabi and Okoromah 2004). Terrestrial plants are a prodigious source of lead compounds, NCEs, and eventually medicine (Fouche et al. 2006), for example, *Catharanthus roseus* (L.) G. Don, Apocynaceae, which yielded the approved chemotherapeutics vincristine and vinblastine (Kumar et al. 2013; Mishra and Verma 2017). *Lessertia frutescens* (L.) Goldblatt & J.C.Manning (syn. *Sutherlandia frutescence* (L.) W:T. Aiton), Fabaceae, found throughout southern Africa's drier parts also shows promise in the early stages of drug discovery and development, with compounds such as canavanine and SU1, a cycloartane-type triterpene glycoside (Van Wyk and Albrecht 2008). Another promising southern African plant is *A. afra* which is a very popular herbal remedy and was shown to possess some interesting *in vitro* bioactivity against HIV, schistosomiasis, and recently lung cancer (Lubbe et al. 2012; Taljaard et al. 2022; van Loggenberg et al. 2022; Vogel et al. 2023).

Due to the recently published antineoplastic activity of *A. afra*, it was decided to review its reported antineoplastic properties as well as some promising lesser-studied plants which showed toxicity in agriculture, or which were used ethnobotanically for the treatment of cancer. When choosing plants from the relatively small South African Kalahari district (shown in Fig. 1a), a selection could be made largely based on their ethnopharmacological importance and/or toxic principles in agricultural settings. The reported cytotoxicity values in this review should be viewed in context of $IC_{50} < 10$ µg/ml, highly active; 10–50 µg/ml, moderate; 50–200 µg/ml, weak; and > 200 µg/ml, inactive (personal communication, USNCI).

## Search Strategy

This review aims to collate available scientific literature regarding the chemical diversity and biological activity, with special emphasis on antiproliferative activity, of *Ammocharis coranica* (Ker Gawl.) Herb., Amaryllidaceae, *Artemisia afra* Jacq., Asteraceae, *Dipcadi glaucum* (Burch. ex Ker Gawl.) Baker, Asparagaceae, *Elephantorrhiza elephantina* (Burch.) Skeels, Fabaceae, *Geigeria ornativa* O.Hoffm., Asteraceae, *Neltuma juliflora* (Sw.) Raf., Fabaceae, and *Senna italica* Mill., Fabaceae, published between 1955 and 2022. Scientific literature published in English in the given time frame was retrieved from scientific databases (Science Direct, Web of Science, Scopus, PubMed, and Google Scholar) as well as several texts and other books regarding medicinal plants, ethnobotany, and toxic plants of veterinary importance in South Africa.

## Discussion

### Plants of Medicinal/Toxicological Interest

A summary of the plants being reviewed, their vernacular names, family, traditional uses, and plant parts used can be found in Table S1, and identified compounds, type of bioassay, and main cytotoxic results can be found in Table S2.

#### *Ammocharis coranica*

**Botany and Traditional Use** The species is widespread throughout southern Africa (Fig. 1b), including in the sandy and sun-drenched area known as the Kalahari. It grows from a drought-resistant deciduous bulb spherical in shape, covered in thinly layered tunics, reaching up to 20 cm in diameter. Broad green leaves about 45 cm long with finely toothed margins lay flat on the surface of the soil. After heavy summer rains, beautiful pink trumpet-shaped flowers (Fig. S1a) with an intensely sweet scent can reach heights of 35 cm (Riddles 2017).

The bulb is used by Zulu traditional healers against mental illnesses such as age-related memory loss, dementia, and

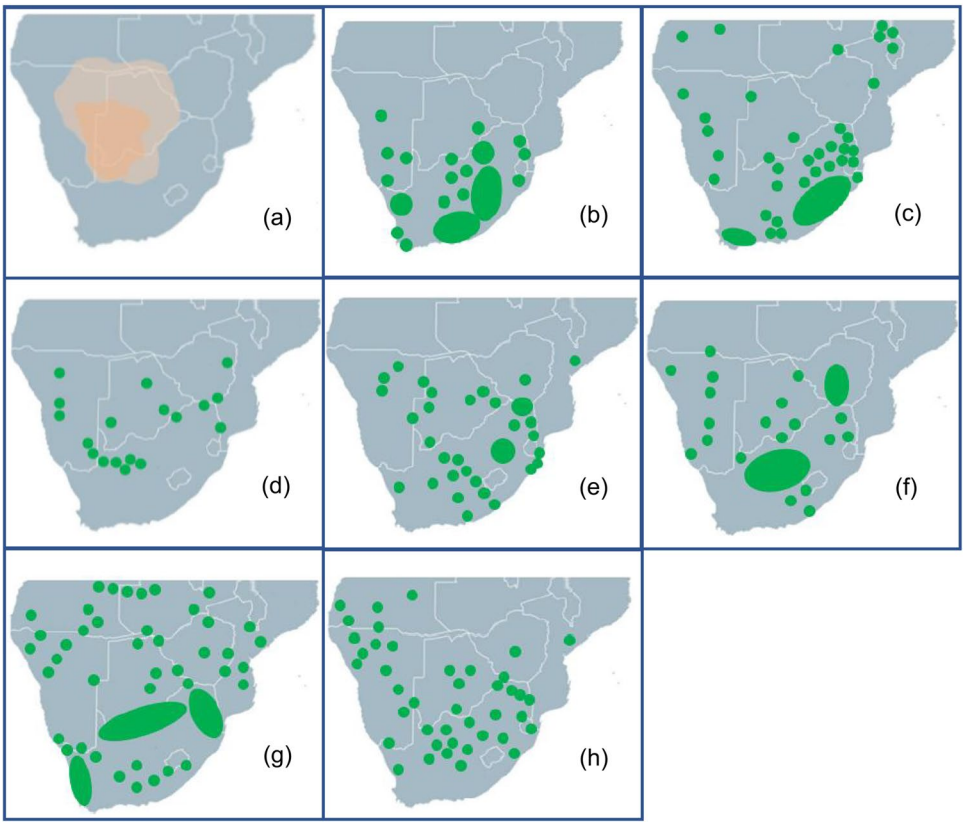
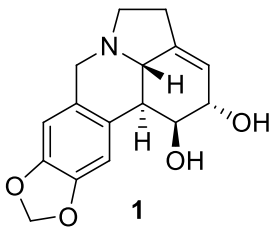



**Fig. 1** The Kalahari region in Southern Africa (**a**) and distribution of *Ammocharis coranica* (**b**), *Artemisia afra* (**c**), *Dipcadi glaucum* (**d**), *Elephantorrhiza elephantina* (**e**), *Geigeria ornativa* (**f**), *Prosopis juliflora* (**g**), and *Senna italica* (**h**)

depression as well as hysteria (Koorbanally et al. 2000). Despite these claims, the active agent has not been identified yet, although it is speculated that crinamine may be the causative agent. The plant is also used as substitute for *Boophone disticha* (L.f.) Herb., Amaryllidaceae, a well-known hallucinogen and arrow poison (Viladomat et al. 1997). Buphanidrine may also be the causative agent for the central nervous system–related effects as had been described by Koorbanally et al. (2000). Furthermore, traditional healers use cooked scales inserted as enemas to "cleanse blood" and apply them to wounds and boils (Louw et al. 2002).

**Chemistry and Bioactivity** Mason et al. (1955) reported the alkaloids lycorine (**1**), caranine, acetylcaranine, and crinamine, to be present (in this bulbous plant), the best known of which is lycorine, a well-documented compound with multiple bioactivities including anti-inflammatory, acetylcholinesterase inhibition, and mild antibacterial, potent antiviral, and antiparasitic activity (Elisha et al. 2013). However, the compound showed most promise against cancer cells. Roy et al. (2018) reported the compound to be highly specific while being very potent and effective at low concentrations though in some cases being less toxic than first-line chemotherapeutic drugs. A total of 26 cancer cell lines have been treated with this compound, yielding very promising results with an $IC_{50}$ value of 0.7 μM (0.21 μg/ml) against human multiple myeloma RPMI-8226. Lycorine was also the most prevalent alkaloid in *A. coranica* with a 0.101% yield based on fresh bulb weight (Wildman 1960).




**1**

When the bulbs were extracted using an alkaloid acid–base extraction technique the final chloroform fraction contained a number of isoquinoline alkaloids, namely, 1-*O*-acetyllycorine, hippadine, 6-alpha-hydroxypowelline, hamayne, and 1-*O*-acetyl-9-*O*-demethylpuviine as well as cycloartane triterpenoids, 24-methylenecycloartan-3 beta-ol, cycloeucalenol, cycloeucalenone, and 24-methylene-pollinastanone (Koorbanally et al. 2000). Furthermore, the new alkaloids golceptine, 6a-hydroxybuphanidrine, and charisine were reported from a new location (Raghoo et al. 2021). Consequently, *A. coranica* is alluring for prospective anticancer lead compounds, NCEs, and maybe even

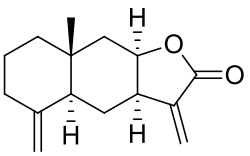
market-available drugs, with lycorine alone warranting further investigation into this plant. This species may yet harbor many other bio-active compounds.

### *Artemisia afra*

**Botany and Traditional Use** With its silver-grey foliage, this perennial shrub is as popular in South African herb gardens as it is in the research community. The thick woody stems carry bushy, untidy clumps of almost fern-like leaves and can grow up to 2 m. This species is found across southern Africa (Fig. 1c) and grows in sand, clay, or loam soils (Van Wyk et al. 1997). The tips of branches produce creamy yellow flowers modest in size in late summer and autumn (Van der Walt 2004).

Watt and Breyer-Brandwijk (1962) reported multiple uses in traditional African medicine but steaming the plant for airway diseases seemed to be the most prevalent. This could be due to volatile compounds as listed by Liu et al. (2009). It is also used by Zulu and Xhosa traditional healers as a remedy for influenza, colds, and coughs. Sesotho and Meru traditional healers use it to treat intestinal worms and reproductive problems (Hutchings 1989; Moteetee and Van Wyk 2011; Mwangi et al. 2017; Moteetee et al. 2019). Furthermore, the dried plant material is often mixed with other medicinal plants to be used by Bapedi traditional healers for the treatment of tuberculosis and opportunistic infections (Semenya and Mayori 2019). Reinforcing the antibacterial effects of this plant, a concoction is used against acne and boils (Mabona and Van Vuuren 2013). It is further said that the leaves are used in an infusion to treat child diseases like measles (Ndhlovu et al. 2021). Finally, prostrate problems were added to the list of treated diseases (Kose et al. 2015).

**Chemistry and Bioactivity** The phytochemistry of *A. afra* was comprehensively reviewed by Liu et al. (2009), Du Toit and van der Kooy (2019), and Shinyuy et al. (2023). Most cytotoxicity studies conducted on *A. afra* remain to be on extract/fraction level and only isoalantolactone (**2**) was tested against cancer cell lines.




**2**

Fouche et al. (2008) reported moderate activity of $CH_2Cl_2$:MeOH extracts of the leaves against renal (TK10), breast (MCF7), and melanoma (UACC62) cancer cells with total growth inhibition (TGI) at 26.62, 15.00, and 9.73 µg/ml, respectively, compared to the positive control, etoposide with a TGI at 27, > 100, and 26.2 µg/ml, respectively. Moreover, the extract displayed good activity against non-small cell lung carcinoma (NCI-H522), melanoma (SK-MEL-5), and colon (HT29) cancer cell lines, with TGI at 13.49, 13.49, and 14.13 µg/ml, respectively.

Ethanol extracts were found to induce apoptosis of promonocytic leukemia (U937) and cervical (HeLa) cancer cells with $IC_{50}$ values of 18.21 and 31.88 µg/ml, respectively (Spies et al. 2012). This apoptosis was observed after a 24-h treatment with plant extract as well as the positive control melphalan ($IC_{50}$ value not reported), further highlighting the possible anticancer characteristics of the plant.

In addition, isoalantolactone was tested against cervical HeLa cancer cells delivering a low $IC_{50}$ value of 8.15 µM (1.89 µg/ml) (Venables et al. 2015). Van Loggenberg et al. (2022) tested infusions prepared from *A. afra* against several lung cancer cell lines and reported $IC_{50}$ values as low as 6 µg/ml, with selectivity index values as high as 10 when tested in Vero non-cancerous cell lines. Similarly, Vogel et al. (2023) screened *A. afra* extracts against various breast cancer cell lines and reported $IC_{50}$ values as low as 4.5 µg/ml. Much more information is needed about this interesting plant, especially following such promise early on in anticancer studies (Taleghani et al. 2020).

### *Dipcadi glaucum*

**Botany and Traditional Use** This hardy annual herb has mostly eluded the interest of researchers. Distributed across Angola, Namibia, Botswana, Zambia, Zimbabwe, and South Africa (Fig. 1d), the species grows from a bulb of about 4 cm in diameter and can reach a height of 120 cm (Vahrmeijer 1981). The blue-green leaves, covered in a waxy powder, are strap-shaped and can grow to be 45 cm long with a width of 4 cm (Fig. S1c). The flowers are green with long pedicels spiralled on the peduncle.

The plant's influence on wildlife and animals in agriculture, however, is so significant, it deserves some attention, exerting its toxic effects on the central nervous system and digestive system of livestock. The plant appears to be highly toxic as its vernacular name in Afrikaans is known as *malkopui* directly translating to "mad-head-onion." Other studies support this but admits the toxin and by extent its mode of action is unknown. Cardiac-glycosides, usually responsible for these effects, are reportedly not present in this species (Botha and Penrith 2008). In this

review, closely related species will be covered as very little research has been conducted on *D. glaucum* with ScienceDirect listing only seven scientific papers in total. A decoction prepared from *D. polyphyllum* Bak. and *D. umbonatum* Bak. is used as a gonorrhea treatment by the Sotho people while the ashed plant is rubbed between the fingers to improve accuracy during hunting and fighting. It is also used as a treatment of pimples. *Dipcadi viride* Moench. is also used as a vegetable by the Sotho people.

**Chemistry and Bioactivity** The chemistry of *D. glaucum* is poorly investigated. It is only reported that it contains no significant levels of alkaloids or glycosides (Al-Najjar 2020). Until recently, the cytotoxicity was investigated neither *in vitro* nor *in vivo*. Notably, given the impact of this plant species' toxicity on ruminant livestock, which is well known, it is surprising that so little research has been conducted to date. The leaves of *Dipcadi serotina* (L.) Medicus contain quercetin and kaempferol while those of *Dipcadi viride* (L.) Moench contain cardiac-glycosides (Williams et al. 1988). Marzouk et al. (2019) identified 22 compounds for the first time in *Dipcadi erythraeum* Webb & Berthel including cardiac-glycosyl flavonoids and derivates of phenolic acid, adding to the list of seven flavonoids previously isolated by El-Shabrawy et al. (2016). Another species, *D. krishnadevarayae*, produces high levels of saponins and tannins, possibly explaining its mild antihelminthic activity (Jyothi et al. 2018).

Antineoplastic activity has been reported from a methanol extract of *D. erythraeum* showing mild activity against MCF7 and colon HCT116 cell lines with cell viabilities of 43.6% and 48.4% when treated at a concentration of 100 µg/ml, but no activity against lung A549 or liver HepG2 cell lines (Marzouk et al. 2019). It highlights that scientific information about *D. glaucum*'s general bioactivity, and more specifically its cytotoxicity, is scarce to non-existent.

### *Elephantorrhiza elephantina*

**Botany and Traditional Use** This perennial sub-shrub has been described as an "underground tree." Aerial stems up to 90 cm tall are unbranched and unarmed harboring dull green, bipinnate compound leaves (Fig. S1d). The dark reddish-brown bark, trunk, and roots grow underground in sandy soil, with the hot, dry Kalahari being the perfect habitat. In fact, this plant is extensively distributed all over southern Africa (Fig. 1e). Yellow to white flowers can be seen between September and November regardless of rainfall and are arranged in axillary, solitary, or clustered racemes (Grobler 2010).

Being a plant of great ethnomedicinal importance, Kose et al. (2015) reported instances of over-harvesting. The roots and rhizomes are used traditionally to treat acne and other skin ailments, even to lighten skin and in the treatment of diarrhea and dysentery (Hutchings 1989; Mabona et al. 2013; Mhlongo and Van Wyk 2019). Along with the application against a myriad of diseases, it is also used in the treatment of breast cancer, tuberculosis and pneumonia, piles, infertility, and even syphilis and herpes (Kose et al. 2015; Maroyi 2017). It should further be noted that the leaves proved to have anti-diabetic and anti-inflammatory activity while remaining non-cytotoxic (Olaokun et al. 2020).

**Chemistry and Cytotoxicity** Using gas chromatography-mass spectrometry (GC–MS) with petroleum ether as an extraction solvent, pregnenolone, α-sitosterol, lupeol, and cycloeucalenol acetate were dereplicated and with methanol as extraction solvent, 2-methylpentanoic acid, 4-oxopentanoic acid, α-methyl-1*H*-imidazole-4-ethanamine, benzothiazole, and but-3-yn-1-yl heptadecylester carbonic acid, where identified (Asong et al. 2019). A review paper further documented the chemical constituents which included anthraquinones, fatty acids, esters, flavonoids, glycosides, phenolic compounds, phytosterols, sugars, saponins, and triterpenoids (Maroyi 2017). Diosgenin and oleanolic acid were isolated from the plant as recently as 2014 by Mpofu et al. (2014), with the compound (−)-epicatechin giving interesting synergistic activity in combination with palmitic acid. The leaves contain alkaloids, triterpenes, phytosterols, and saponins, while for the roots, terpenoids, phlabotannins, saponins, and alkaloids could not be identified (Kudumela and Masoko 2018; Olaokun et al. 2020).

Leaves are used traditionally in the treatment of breast cancer (Raimi et al. 2020). A cytotoxicity study using African green monkey (Vero) cells testing acetone extracts of the entire plant showed a $LC_{50}$ of 416.4 µg/ml, which falls far outside the cutoff point of $LC_{50} < 200.0$ µg/ml suggested by the NCI for plant extracts to be considered cytotoxic (Kudumela et al. 2018). A follow-up study was conducted the following year, using the same Vero cell line, and it was found that methanol extracts of the rhizomes had an $LC_{50}$ value of 9.4 µg/ml which falls well within the range of the NCI (Asong et al. 2019). By means of the brine shrimp assay, methanolic extracts of the plant showed great cytotoxic activity with an $LC_{50}$ of 1.8 µg/ml, whereas an aqueous extract exhibited only mild toxicity (Mpofu et al. 2014).

Cell line assays were carried out with the acetone, ethanol, cold water, and hot water extract of the leaves, against H4IIE hepatoma, a tumor cell line as well as C2C12 myocytes and myotubules, stages of muscle cells, delivering $IC_{50}$'s between 697 and > 1000 µg/ml, between 87 and

256 µg/ml, and > 100 µg/ml, respectively, compared to the positive control doxorubicine with 15.53, 2.75, and 176 µg/ml, respectively. In summary, while extracts were not active against hepatoma cells, the highest toxicity recorded for the cold water extract against myocytes was an $IC_{50}$ of 87 µg/ml (Olaokun et al. 2020).

### *Geigeria ornativa*

**Botany and Traditional Uses** Common in southern Africa (Fig. 1f), this perennial herb grows low and keeps close to the ground (Vahrmeijer 1981). The stem is scarce and usually branched, angular, flattened, and ribbed as it ascends. The leaves are shallowly toothed and located along the stem while forming a basal rosette, protruding up to 10 cm. Flowers are bright yellow and usually located where stems branch (Fig. S1b). No published literature is available regarding the traditional uses of *G. ornativa*. According to Watt and Breyer-Brandwijk (1962), the Sotho people used *G. africana* Gr. as an antiparasitic agent while a decoction of *G. aspera* Harv. is used for a remedy of giddiness.

**Chemistry and Cytotoxicity** Ingestion of the plant result in *vermeersiekte* (vomiting disease) and is marked by hepatotoxicity and photosensitivity (Mbaveng et al. 2014). It is believed that the toxin is furanosesquiterpenoids targeting striated muscle, but these compounds have not yet been identified in this species (Botha and Penrith 2008). The plant has been neglected in the research world, but other species from the genus *Greigeria* have enjoyed some attention. A good example is *Greigeria burkei* (Benth.) S.A.O'Donnell & G.P.Lewis delivering the sesquiterpine lactones geigerin, vermeeric acid, and vermeerin. Biological effects are reported against emesis, respiratory suppression, and bacteria (Zdero and Bohlmann 1989; Bohlmann et al. 1982; Coleman et al. 1984; Awouafack et al. 2013; Ndhlala et al. 2013). Geigerin showed a mild apoptotic affect against murine myoblast cells (C2C12) with cell viability of 31.2% after 72 h at 5314 mM/1321.6 µg/ml (Botha et al. 2017).

### *Prosopis juliflora*

**Botany and Traditional Use** This drought-resistant deciduous shrub is an invasive, but naturalised, species in southern Africa, flourishing in semi-arid and arid tracts of tropical and sub-tropical areas, including the Kalahari region of South Africa (Fig. 1g) (Sawal et al. 2004; Heshmati et al. 2019). Reaching a height of up to 15 m, its drooping branches carry feathery foliage on straight, paired spined twigs (Fig. S1f). This plant has enjoyed much attention from medicinal researchers until the 1980s, followed by a slight hiatus, but is gaining momentum once again (Ukande et al. 2019). Popular among Indian Ayurvedic traditional healers, it is known for its use in inflammatory illnesses such as rheumatism and as a remedy for scorpion stings and snake bites (Ahmad et al. 1989).

**Chemistry and Cytotoxicity** Two piperadine alkaloids were first isolated from the leaves in 1989, juliprosinene and juliflorinine, adding to the already known juliflorine, julifloricine, julifloridine, and juliprosipine (Ahmad et al. 1989). Dhivya et al. (2018) reported six new compounds and several known compounds from the hexane extracts of the seed pods, namely *N*-hexadecanoic acid, 9,12-octadecadionoic acid methyl ester, 9,12-octadecadienoic acid methyl ester, 12-tridecynoic acid methyl ester, 9-octadecyne, and squalene. Other compounds identified include prosoflorine, juliprosine, (−)-mesquitol, 7,3,4-trihydroxy-3-methoxyflavone, catechin, dehydroabietic acid, patulitrin, schaftoside, 24-methylencycloartan-3-one, zerumbone, *N*-β-chloropropionyltryptamine, cassine, prosophyline, tryptamine, β-phenylthylamine, indolizidine, myo-inositol-4*C*-methyl, and linoleic acid (Ukande et al. 2019).

Malik et al. (2018) reported 1-methoxy-2-propyl acetate, fluoro-ethyne, cyclobutanol, 1-methyldecylamine, 3-hydroxybutanal, cyclopropaneoctanoic acid, methyl 5-(2-undecylcyclopropyl) pentanoate, ergosterol acetate, maymyrsine, cycloartenol, carpesterol benzoate, and 9-(2-oxiranyl)-1-nonanol. The authors summarized compounds with "confirmed" antineoplastic effects as pentanal, butyramide, *N*-hexadecanoic acid, and hydroxyurea. The authors did not test these compounds for bioactivity but instead referred to a terpenoid database that could not be found.

Patulitrin, a flavonoid, was isolated from the fruit (Wassel et al. 1972), whereas alkaloid extracts from the leaves exhibited $IC_{50}$ values of 90.5, 42.5, and 20 µg/ml after 24, 48, and 72 h, respectively, against the human lymphoblast MOLT-4 cell line, while an $IC_{50}$ could not be determined against human normal mitogen stimulated T-lymphocytes, due to very low growth inhibition, indicating high selectivity (Sathiya and Muthuchelian 2011).

The ethyl acetate extract of the leaves led, after 72 h, to $IC_{50}$s of 18.17, 33.10, and 41.90 µg/ml against human breast MCF-7, liver HePG2, and colorectal cancer LS-174 T cell lines, respectively. Interestingly, these extracts were described as cytotoxic by means of necrosis rather than apoptosis. Two years later, using the same cell lines (MCF-7, HePG2, and LS-174 T) in the same order, the methanolic and butanolic extract of the leaves led to $IC_{50}$ values of 8.10, 18.04, and 16.70 µg/ml as well as 5.17, 32.80, and 12.50 µg/ml, respectively (Elbehairi et al. 2020; Abbas et al. 2022). Notably, in summary, significant activity is reported from the butanolic extract of the leaves with an $IC_{50}$ of 5.17 µg/ml against human breast MCF-7 cell line.

B16F10 (skin melanoma) is an aggressively metastatic cell line and appears to be resistant to many modern chemotherapeutics. Therefore, it is compelling then that methanolic extracts of the leaves yielded an $IC_{50}$ value of 17 µg/ml with the MTT cell viability assay (Raju 2020). Focusing on breast cancer, the same methanolic leaf extract proved to be more effective against MDA-MB-231 with an $IC_{50}$ value of 16.8 µg/ml than against MCF-7 cells with an $IC_{50}$ of 19.4 µg/ml. The methanolic leaf extract also showed toxicity to (normal) human keratinocyte HaCat cells with an $IC_{50}$ of 24.1 µg/ml (Utage et al. 2018). $GI_{50}$ estimations of the extract against the cancer cell lines (MOLT-4, oral (KB), and HeLa) were found to be 46.44, 46.12, and 45.61 µg/ml at 24-h exposure; 32.35, 32.25, and 32.08 µg/ml at 48-h exposure; and 23.75, 23.51, and 22.65 µg/ml at 72-h exposure, respectively (Sathiya and Muthuchelian 2010).

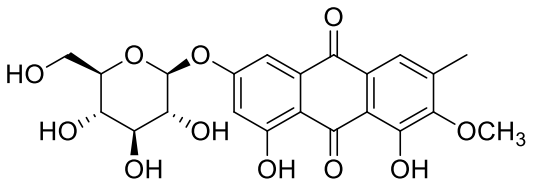
### *Senna italica*

**Botany and Traditional Use** This ascending perennial herb or small shrub, growing up to 60 cm tall from a woody base, is actually a legume. The leaves are interesting with pairs of dark olive-colored leaflets (Fig. 1e) housing a small reddish gland between each leaflet pair, up to 3 cm long and 2 cm in width. The sandy Kalahari soil is the perfect habitat for this species, but it can be found throughout the entire southern Africa (Fig. 1h). Flowers are yellow to orange in color, around 10 cm long, and abundant when the plant is blooming.

In traditional medicine, crude extracts of the plant are used to treat tuberculosis and opportunistic infections as well as chronic cough (Kuete et al. 2013; Semenya and Mayori 2019). The roots are used to treat gonorrhea, and aerial parts used in the treatment of intestinal tumors and urinary tract infections as well as influenza (Mulaudzi et al. 2015; Gololo et al. 2016; Cock and van Vuuren 2020). The roots are powdered and used in the treatment of gonorrhea (Mongalo et al. 2017). Less frequently, roots are applied topically to treat boils (Mabona and van Vuuren 2013).

**Chemistry and Cytotoxicity** A chemical screening of a hexane leaf extract using GC–MS provided insight and possible explanation for this plant's pharmacological activity with the following compounds identified: phytol, 1,2-benzenedicarboxylic acid, mono (2-ethylheptyl) ester, N-tetracontane, 13-docosenamide, squalene, 1-heptacosanol, oxirane, (α)-tocopherol-ß-D-mannoside, stigmasterol, (ɣ)-sitosterol, and lupeol (Gololo et al. 2016). Along with above compounds, physcion, emodin, 2-methoxy-emodin-6-*O*-β-D-glucopyranoside, tinnevellin, quercetin, rutin, and 1,6,8-trihydroxy-3-methoxy-9,10-dioxo-9,10-dihydroanthracene were isolated from aerial parts of plants grown in Sudan (Khalaf et al. 2019). From the root extract of the plant, resveratrol was isolated as the most abundant compound, at 0.018% of the weight (Mokgotho et al. 2013).

A crude extract obtained from the aerial parts of the plant using 80% ethanol displayed an $IC_{50}$ of 7.13 µg/ml against the leukemia CCRF-CEM cell line, compared to doxorubicin with 0.11 µg/ml (Kuete et al. 2013). Methylene chloride extracts of the aerial parts, on the other hand, showed potent antineoplastic activity. $IC_{50}$ values were calculated for HepG-2 at 16.9 µg/ml, HeLa at 17.4 µg/ml, PC3 at 18.3 µg/ml, and MCF-7 at 14.2 µg/ml compared to that of the positive control 5-fluorouracil with 7.9, 4.8, 8.3, and 5.4 µg/ml respectively (Madkour et al. 2017). 2-Methoxy-emodin-6-*O*-β-D-glucopyranoside (**3**) presented with moderate activity against human liver cancer Hep G2 with $IC_{50}$ of 57.5 µg/ml and breast cancer MCF-7 with $IC_{50}$ of 42.3 µg/ml (Khalaf et al. 2019). According to the USNCI, crude extracts can be considered to have high activity when their $IC_{50}$ values are less than 10 µg/ml.




**3**

Caution should be taken in interpreting the presented results in that all research reported were based on pre-clinical experiments which suffer from many drawbacks. These drawbacks may be exemplified by the wide and unrelated bioactivity that is reported for plant species, such as for *A. afra*, which might indicate that it contains compounds known to generate false positives by reacting with components commonly used across the various *in vitro* bioassays employed in many of these studies. Usually when a plant species shows a broad range of unrelated bioactivities, it is considered a panacea and future research should keep in mind that it might contain common compounds that generate false positive results. Bisson et al. (2016) investigated this phenomenon and designated false positive natural products as "invalid metabolic panaceas." Isolating and identifying the true actives and conducting properly designed *ex vivo/in situ* studies followed by clinical studies, if the evidence supports this, should therefore be conducted.

The reviewed plant species do however show some interesting results. If their biological and toxicological effects could serve as incentive for further investigation, *D. glaucum* and *G. ornativa* deserve more attention in the research community. Not only may their impact on mammal toxicity yield

interesting cytotoxic compounds for future cancer studies, but also identification of their toxic principles might lead to a better understanding of their mode of action and might even lead to development of effective therapeutical phytomedicines. Lycorine has been identified in *A. coranica* and seems to have potent antineoplastic activity of 0.21 µg/ml. Although lycorine is more commonly known to occur in daffodils (*Narcissus* spp.), it is currently considered to be a promising drug lead for the future development of effective cancer treatments. It could be interesting to explore its central nervous system (CNS) effects, but the plant's scarcity could prove challenging for future research and a better source would therefore clearly be the rather common horticultural *Narcissus* spp. Research in *A. coranica* should therefore focus on identifying even more potent derivatives which may occur in the plant.

The ethnomedicinal use, biological effects, and chemical fingerprint of *E. elephantina* have been documented but reports on the antineoplastic properties require more studies for clarity. Much remains unknown about the aerial parts of the plant, pleading for additional attention, and despite the published underwhelming antineoplastic activity, a patent has been filed by the Council for Scientific and Industrial Research (CSIR) with Patent No. US 9061023 B2 on extracts of this plant for treatment and management of benign prostatic hyperplasia (BPH) (Maharaj et al. 2019). This is due to the fact the extract inhibits 5-alpha-reductase, the enzyme which converts testosterone to dihydrotestosterone which in turn is one of the causal elements to the progression of BPH.

*Artemisia afra* shows promise with a selectivity index (SI) of 10 and $IC_{50}$ values as low as 6 µg/ml for a chemically complex infusion. The recently identified prenylated coumarin, umbelliprenin, has also been tested for its antineoplastic properties *in vitro* and *in vivo* and might be an interesting class of compounds to conduct further studies. Isoalantolactone identified in *A. afra* shows much promise with an $IC_{50}$ of 1.89 µg/ml and should therefore be further investigated. Specific extracts from *P. juliflora* showed impressive antineoplastic activity, but it remains on extract level and hence research into identifying the active compounds is needed. The naturalized *P. juliflora* might become an economically valuable resource which in turn can lead to containment of its aggressive invasive nature.

## Perspectives and Future Directions

Natural products also present challenges from a drug development and discovery point of view, with technical barriers in characterization and optimization. Nevertheless, several advancements in scientific technologies are addressing such challenges and giving rise to new opportunities. For example, at Pharmacen, North-West University, a new 3D cancer model has been established (Van der Merwe et al. 2022). The model aims to bridge the gap between the normal *in vitro* cancer cell line testing (2D) and *in vivo* animal testing by simulating the 3D cellular environment of cancer cells. This model will be used in future experiments to study the most promising plant extracts and isolated compounds in order to gain a better understanding of their true potency and their mechanism of action.

## Conclusion

Identification of active constituents, more in-depth *ex vivo*/*in situ* experiments, and eventually clinical trials should be conducted on the most promising plant extracts and/or pure compounds identified therein.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s43450-024-00546-3.

**Author Contribution** DV: conceptualized, designed, and wrote the manuscript. CG and FVK have substantively revised the manuscript. All authors have read and agreed to the published version of the manuscript.

**Funding** Open access funding provided by North-West University.

**Data Availability** Not applicable.

## Declarations

**Ethics Approval** Not applicable.

**Competing Interests** The authors declare no competing interests.



## References

Abbas AM, Ng KY, Al-Kahtani MA, lfaifi MY, Alrumman SA, Elbehairi SEI, Ahmed AE (2022) Apoptosis and cell cycle analysis of the human cancer cell lines; breast Michigan Cancer Foundation 7, LS-174T colon and HePG2 liver in response to the methanolic and butanolic extracts of *Prosopis juliflora*. Sci Adv Mater 14:130-140. https://doi.org/10.1166/sam.2022.4183

Afolabi BB, Okoromah CAN (2004) Intramuscular artemether for treating severe malaria. Cochrane Database Syst Rev Issue 4:CD004391. https://doi.org/10.1002/14651858.CD004391.pub2

Ahmad VU, Sultana A, Qazi S (1989) Alkaloids from the leaves of *Prosopis juliflora*. J Nat Prod 52:497–501. https://doi.org/10.1021/np50063a005

Al-Najjar HA (2020) Phytochemical investigation of *Dipcadi ervthraeum*. Med J Cairo Univ 88:761–764. https://doi.org/10.21608/mjcu.2020.104883

Asong JA, Amoo SO, McGaw LJ, Nkadimeng SM, Aremu AO, Otang-Mbeng W (2019) Antimicrobial activity, antioxidant potential, cytotoxicity and phytochemical profiling of four plants locally used against skin diseases. Plants 8:350. https://doi.org/10.3390/plants8090350

Awouafack MD, Tane P, Kuete V, Eloff JN (2013) Sesquiterpenes from the medicinal plants of Africa. In: Medicinal plant research in Africa 2nd Edition, Elsevier 33–103. https://doi.org/10.1016/B978-0-12-405927-6.00002-3

Bisson J, McAlpine JB, Friesen JB, Chen S-N, Graham J, Pauli GF (2016) Can invalid bioactives undermine natural product-based drug discovery? J Med Chem 59:1671–1690. https://doi.org/10.1021/acs.jmedchem.5b01009

Bohlmann F, Zdero C, Ahmed M (1982) New sesquiterpene lactones, geranyllinalol derivatives and other constituents from *Geigeria* species. Phytochemistry 21:1679–1691. https://doi.org/10.1016/S0031-9422(82)85040-1

Botha CJ, Penrith ML (2008) Poisonous plants of veterinary and human importance in southern Africa. J Ethnopharmacol 119:549–558. https://doi.org/10.1016/j.jep.2008.07.022

Botha CJ, Clift SJ, Ferreira GC, Masango MG (2017) Geigerin-induced cytotoxicity in a murine myoblast cell line (C2C12). Onderstepoort J Vet Res 8:a1465. https://doi.org/10.4102/ojvr.v84i1.1465

Cock IE, Van Vuuren SF (2020) The traditional use of southern African medicinal plants for the treatment of bacterial respiratory diseases: a review of the ethnobotany and scientific evaluations. J Ethnopharmacol 263:113204. https://doi.org/10.1016/j.jep.2020.113204

Coleman PC, Potgieter DJJ, Van Asegen CH, Vermeulen NMJ (1984) Flavonoids of *Geigeria*. Phytochemistry 23:1202–1203. https://doi.org/10.1016/S0031-9422(00)82648-5

Cooper GM (2000) The cell: a molecular approach. 2nd ed. Sunderland (MA): Sinauer Associates; The development and causes of cancer. https://www.ncbi.nlm.nih.gov/books/NBK9963/. Accessed Nov 2023

Dhivya K, Vengateswari G, Arunthirumeni M, Karthi S, Senthil-Nathan S, Shivakumar MS (2018) Bioprospecting of *Prosopis juliflora* (Sw.) DC seed pod extract effect on antioxidant and immune system of *Spodoptera litura* (Lepidoptera:Noctuidae). Physiol Mol Plant Pathol 101:45–53. https://doi.org/10.1016/j.pmpp.2017.09.003

Du Toit A, Van der Kooy F (2019) *Artemisia afra*, a controversial herbal remedy or a treasure trove of new drugs? J Ethnopharmacol 244:112127. https://doi.org/10.1016/j.jep.2019.112127

Elbehairi SEI, Ahmed AE, Alshati AA, Al-Kahtani MA, Alfaifi MY, Alsyaad KM, Abbas AM (2020) *Prosopis juliflora* leave extracts induce cell death of MCF-7, HEPG2, and LS-174T cancer cell lines. Excli J 19:1282–1294. https://doi.org/10.17179/excli2020-2830

Elisha IL, Elgorashi EE, Hussein AA, Duncan G, Eloff JN (2013) Acetylcholinesterase inhibitory effects of the bulb of *Ammocharis coranica* (Amaryllidaceae) and its active constituent lycorine. S Afr J Bot 85:44–47. https://doi.org/10.1016/j.sajb.2012.11.008

El-Shabrawy MO, Marzouk MM, Kawashty SA, Hosni SA, El Garf LA, Saleh NAM (2016) Flavonoid constituents of *Dipcadi erythraeum* Webb. & Berthel. Asian Pac J Trop Dis 6:404–405. https://doi.org/10.1016/S2222-1808(15)61056-8

Fouche G, Khorombi E, Kolesnikova N, Maharaj VJ, Nthambeleni R, van der Merwe M (2006) Investigation of South African plants for anticancer properties. Pharmacologyonline 3:494–500

Fouche G, Cragg GM, Pillay P, Kolesnikova N, Maharaj VJ, Senabe J (2008) *In vitro* anticancer screening of South African plants. J Ethnopharmacol 119:455–461. https://doi.org/10.1016/j.jep.2008.07.005

Gololo SS, Shai LJ, Agyei NM, Mogale MA (2016) Effect of seasonal changes on the quantity of phytochemicals in the leaves of three medicinal plants from Limpopo province, South Africa. J Pharmacogn Phytother 8:168–172. https://doi.org/10.5897/JPP2016.0408

Grobler A (2010) *Elephantorrhiza elephantina*. PlantZAfrica.com. https://pza.sanbi.org/elephantorrhiza-elephantina. Accessed 25 March 2024

Heshmati I, Khorasani N, Shams-Esfandabad B, Riazi B (2019) Forthcoming risk of *Prosopis juliflora* global invasion triggered by climate change: implications for environmental monitoring and risk assessment. Environ Monit Assess 191:72. https://doi.org/10.1007/s10661-018-7154-9

Hutchings A (1989) Observations on plant usage in Xhosa and Zulu medicine. Bothalia 19:225–235

Jyothi VM, Salamma S, Bhargav E, Chaitanya MVNL, Rao BRP (2018) Phytochemical screening, antihelminthic activity and antioxidant potential of *Dipcadi krishnadevarayae* (Aparagaceae). Int J Pharm Biol Sci 8:322–338

Khalaf OM, Ghareeb MA, Saad AM, Madkour HMF, El-Ziaty AK, Abdel-Aziz MS (2019) Phenolic constituents, antimicrobial, antioxidant, and anticancer activities of ethyl acetate and *n*-butanol extracts of *Senna italica*. Acta Chromatogr 31:138–145. https://doi.org/10.1556/1326.2018.00412

Koorbanally N, Mulholland DA, Crouch N (2000) Alkaloids and triterpenoids from *Ammocharis choranica* (Amaryllidaceae). Phytochemistry 54:93–97. https://doi.org/10.1016/s0031-9422(00)00039-x

Kose LS, Moteetee A, Van Vuuren S (2015) Ethnobotanical survey of medicinal plants used in the Maseru district of Lesotho. J Ethnopharmacol 170:184–200. https://doi.org/10.1016/j.jep.2015.04.047

Kudumela RG, Masoko P (2018) *In vitro* assessment of selected medicinal plants used by the Bapedi community in South Africa for treatment of bacterial infections. J Evid Based Integr Med 2018:23. https://doi.org/10.1177/2515690X18762736

Kudumela RG, McGaw LJ, Masoko P (2018) Antibacterial interactions, anti-inflammatory and cytotoxic effects of four medicinal plant species. BMC Complement Med Ther 18:199. https://doi.org/10.1186/s12906-018-2264-z

Kuete V, Wiench B, Alsaid MS, Alyahya MA, Fankam AG, Shahat AA, Efferth T (2013) Cytotoxicity, mode of action and antibacterial activities of selected Saudi Arabian medicinal plants. BMC Complement Med Ther 13:354. https://doi.org/10.1186/1472-6882-13-354

Kumar A, Patil D, Rajamohanan PR, Ahmad A (2013) Isolation, purification and characterization of vinblastine and vincristine from endophytic fungus *Fusarium oxysporum* isolated from *Catharanthus roseus*. Plos One 8:71805. https://doi.org/10.1371/journal.pone.0071805

Liu NQ, Van der Kooy F, Verpoorte R (2009) *Artemisia afra*: a potential flagship for African medicinal plants? S Afr J Bot 75:185–195. https://doi.org/10.1016/j.sajb.2008.11.001

Louw CAM, Regnier L, Korsten L (2002) Medicinal bulbous plants of South Africa and their traditional relevance in the control of infectious diseases. J Ethnopharmacol 82:147–154. https://doi.org/10.1016/s0378-8741(02)00184-8

Lubbe A, Seibert I, Klimkait T, Van der Kooy F (2012) Ethnopharmacology in overdrive: the remarkable anti-HIV activity of *Artemisia annua*. J Ethnopharmacol 141:854–859. https://doi.org/10.1016/j.jep.2012.03.024

Mabona U, Van Vuuren SF (2013) Southern African medicinal plants used to treat skin diseases. S Afr J Bot 87:175–193. https://doi.org/10.1016/j.sajb.2013.04.002

Mabona U, Viljoen A, Shikanga E, Marston A, van Vuuren S (2013) Antimicrobial activity of southern African medicinal plants with dermatological relevance: from an ethnopharmacological screening approach, to combination studies and the isolation of a bioactive compound. J Ethnopharmacol 148:45–55. https://doi.org/10.1016/j.jep.2013.03.056

Madkour HMF, Ghareeb MA, Abdel-Aziz MS, Khalaf OM, Saad AM, El-Ziaty AK, Abdel-Mogib M (2017) Gas chromatography-mass spectrometry analysis, antimicrobial, anticancer and antioxidant activities of n-hexane and methylene chloride extracts of *Senna italica*. J Appl Pharm Sci 7:23–32. https://doi.org/10.7324/JAPS.2017.70604

Maharaj VJ, Naidoo-Maharaj D, Fouche G, Mianda SM (2019) Are scientists barking up the wrong tree to "scientifically validate" traditional medicines? S Afr J Bot 126:58–64. https://doi.org/10.1016/j.sajb.2019.06.010

Malik SK, Ahmed M, Khan F (2018) Identification of novel anticancer terpenoids from *Prosopis juliflora* (Sw) DC (Leguminosae) pods. Trop J Pharm Res 17:661–668. https://doi.org/10.4314/tjpr.v17i4.14

Maroyi A (2017) *Elephantorrhiza elephantina*: traditional uses, phytochemistry, and pharmacology of an important medicinal plant species in southern Africa. Evid Based Compl Alt Med 2017:6403905. https://doi.org/10.1155/2017/6403905

Marzouk MM, Elkhateeb A, Latif RRA, Abdel-Hameed ESS, Kawashty SA, Hussein SR (2019) *C*-glycosyl flavonoids-rich extract of *Dipcadi erythraeum* Webb & Berthel. bulbs: phytochemical and anticancer evaluations. J Appl Pharm Sci 9:94–98. https://doi.org/10.7324/japs.2019.90613

Mason LH, Puschett ER, Wildman WC (1955) Alkaloids of the Amaryllidaceae. IV. Crystalline alkaloids of *Ammocharis coranica* (Ker-Gawl.) Herb., *Brunsvigia rosea* (Lam.) Hannibal and two *Crinum* species. J Am Chem Soc 5:1253–1256. https://doi.org/10.1021/ja01610a046

Mbaveng AT, Hamm R, Kuete V (2014) 19 - Harmful and protective effects of terpenoids from African medicinal plants. In: Kuete V (ed.) Toxicological survey of African medicinal plants. Elsevier 557–576. https://doi.org/10.1016/B978-0-12-800018-2.00019-4

Mhlongo LS, Van Wyk BE (2019) Zulu medicine ethnobotany: new records from the Amandawe area of KwaZulu-Natal, South Africa. S Afr J Bot 122:266–290. https://doi.org/10.1016/j.sajb.2019.02.012

Mishra JN, Verma NK (2017) A brief study of *Catharanthus roseus*: a review. Int J Res Pharm Sci 2:20–23

Mokgotho MP, Gololo SS, Masoko P, Mdee LK, Mbazima V, Shai LJ, Mampuru L (2013) Isolation and chemical structural characterisation of a compound with antioxidant activity from the roots of *Senna italica*. Evid Based Compl Alt Med 2013:519174. https://doi.org/10.1155/2013/519174

Mongalo NI, McGaw LJ, Finnie JF, Van Staden J (2017) Pharmacological properties of extracts from six South African medicinal plants used to treat sexually transmitted infections (STIs) and related infections. S Afr J Bot 112:290–295. https://doi.org/10.1016/j.sajb.2017.05.031

Moteetee A, Van Wyk BE (2011) The medical ethnobotany of Lesotho: a review. Bothalia 41:209–228. https://doi.org/10.4102/abc.v41i1.52

Moteetee A, Moffet RO, Seleteng-Kose L (2019) A review of the ethnobotany of the Basotho of Lesotho and the Free State Province of South Africa (South Sotho). S Afr J Bot 122:21–56. https://doi.org/10.1016/j.sajb.2017.12.012

Mpofu SJ, Msagati TAM, Krause RWM (2014) Cytotoxicity, phytochemical analysis and antioxidant activity of crude extracts from rhizomes of *Elephantorrhiza elephantina* and *Pentanisa prunelloides*. Afr J Trad Compl Alt Med 11:34–52. https://doi.org/10.4314/ajtcam.v11i1.6

Mulaudzi RB, Ndhlala AR, Van Staden J (2015) Ethnopharmacological evaluation of a traditional herbal remedy used to treat gonorrhoea in Limpopo province, South Africa. S Afr J Bot 97:117–122. https://doi.org/10.1016/j.sajb.2014.12.007

Mwangi VI, Mumo RM, Nyachieo A, Onkoba N (2017) Herbal medicine in the treatment of poverty associated parasitic diseases: a case of sub-Saharan Africa. J Herb Med 10:1–7. https://doi.org/10.1016/j.hermed.2017.03.002

Ndhlala AR, Ncube B, Okem A, Mulaudzi RB, Van Staden J (2013) Toxicology of some important medicinal plants in southern Africa. Food Chem Toxicol 62:609–621. https://doi.org/10.1016/j.fct.2013.09.027

Ndhlovu PT, Omotayo AO, Otang-Mbeng W, Aremu AO (2021) Ethnobotanical review of plants used for the management and treatment of childhood diseases and well-being in South Africa. S Afr J Bot 137:197–215. https://doi.org/10.1016/j.sajb.2020.10.012

Newman DJ, Cragg GM (2020) Plant endophytes and epiphytes: burgeoning sources of known and unknown cytotoxic and antibiotic agents? Planta Med 86:891–905. https://doi.org/10.1055/a-1095-1111

O'Connor R (2007) The pharmacology of cancer resistance. Anticancer Res 27:1267–1272. ISSN 1791–7530

Olaokun OO, Alaba AE, Ligege K, Mkolo NM (2020) Phytochemical content, antidiabetes, anti-inflammatory antioxidant and cytotoxic activity of leaf extracts of *Elephantorrhiza elephantina* (Burch.) Skeels. S Afr J Bot 128:319–325. https://doi.org/10.1016/j.sajb.2019.11.030

Raghoo M, Crouch NR, Koorbanally NA (2021) A novel and unusual tetramethoxylated crinine alkaloid from *Ammocharis coranica* (Amaryllidaceae). S Afr J Bot 137:451–454. https://doi.org/10.1016/j.sajb.2020.11.012

Raimi IO, Koaopa BG, Mugivhisa LL, Lewu FB, Amoo SO, Olowoyo JO (2020) An appraisal of documented medicinal plants used for the treatment of cancer in Africa over a twenty-year period (1998–2018). J Herb Med 23:100371. https://doi.org/10.1016/j.hermed.2020.100371

Raju NG (2020) Novel leads from *Prosopis juliflora* (Sw.) arrest the growth of B16F10 melanoma cancer cells by inducing apoptosis and down regulating the cell proliferating signalling pathway. Cancer Res 80:6551. https://doi.org/10.1016/j.jep.2023.116472

Riddles R (2017) *Ammocharis coranica*. PlantZAfrica.com. https://pza.sanbi.org/ammocharis-coranica. Accessed 25 March 2024

Roy M, Liang L, Xiao X, Feng P, Ye M, Liu J (2018) Lycorine: a prospective natural lead for anticancer drug discovery. Biomed Pharmacother 107:615–624. https://doi.org/10.1016/j.biopha.2018.07.147

Sathiya M, Muthuchelian K (2010) Evaluation of antioxidant and antitumor potentials of *Prosopis juliflora* DC. leaves *in vitro*. Pharmacologyonline 2:328–343

Sathiya M, Muthuchelian K (2011) Anti-tumor potential of total alkaloid extract of *Prosopis juliflora* DC. leaves against Molt-4 cells *in vitro*. Afr J Biotechnol 10:8881–8888. https://doi.org/10.5897/AJB10.875

Sawal RK, Ratan R, Yadav SBS (2004) Mesquite (*Prosopis juliflora*) pods as feed resource for livestock – a review. Anim Biosci 5:719–725. https://doi.org/10.5713/ajas.2004.719

Semenya SS, Mayori A (2019) Ethnobotanical survey of plants used by Bapedi traditional healers to treat tuberculosis and its opportunistic infections in the Limpopo Province, South Africa. S Afr J Bot 122:401–421. https://doi.org/10.1016/j.sajb.2018.10.010

Shinyuy LM, Loe GE, Jansen O, Mamede L, Ledoux A, Noukimi SF, Abenwie SN, Ghogomu SM, Souopgui J, Robert A, Demeyer K,

Frederich M (2023) Secondary metabolites isolated from *Artemisia afra* and *Artemisia annua* and their anti-malarial, anti-inflammatory and immunomodulating properties—pharmacokinetics and pharmacodynamics: a review. Metabolites 13:613. https://doi.org/10.3390/metabo13050613

Spies L, Koekemoer TC, Sowemimo AA, Goosen ED, Van de Venter M (2012) Caspase-dependent apoptosis is induced by *Artemisia afra* Jacq. ex Willd in a mitochondria-dependent manner after G2/M arrest. S Afr J Bot 84:104–109. https://doi.org/10.1016/j.sajb.2012.10.007

Taleghani A, Emami SA, Tayarani-Najaran Z (2020) *Artemisia:* a promising plant for the treatment of cancer. Bioorg Med Chem 28:115180. https://doi.org/10.1016/j.bmc.2019.115180

Taljaard L, Probst A, Tornow R, Keiser J, Haynes R, Van der Kooy F (2022) *In vitro* antischistosomal activity of *Artemisia annua* and *Artemisia afra* extracts. Phytomed plus 2:100279. https://doi.org/10.1016/j.phyplu.2022.100279

Ukande M, Shaikh S, Murthy K, Shete R (2019) Review on pharmacological potentials of *Prosopis juliflora*. J Drug Deliv Ther 9:755–760. https://doi.org/10.22270/jddt.v9i4-s.3372

Utage BG, Patole MS, Nagvenkar PV, Kamble SS, Gacche RN (2018) *Prosopis juliflora* (SW), DC induces apoptosis cell cycle arrest in triple negative breast cancer cells: *in vitro* and *in vivo* investigations. Oncotarget 9:30304–30323. https://doi.org/10.18632/oncotarget.25717

Vahrmeijer J (1981) Gifplante van Suider-Afrika wat veeverliese veroorsaak, 1st edn. Tafelberg, Cape Town

Van der Merwe L, Svitina H, Willers C, Wrzesinski K, Gouws C (2022) A novel NCI-H69V small cell lung cancer functional mini-tumor model for future treatment screening applications. Biotech Prog 38:e3253. https://doi.org/10.1002/btpr.3253

Van Wyk BE, Albrecht C (2008) A review of the taxonomy, ethnobotany, chemistry and pharmacology of *Sutherlandia frutescens* (Fabaceae). J Etnopharmacol 119:620–629. https://doi.org/10.1016/j.jep.2008.08.003

Van Loggenberg S, Willers C, Van der Kooy F, Gouws C, Hamman JH, Steyn JD (2022) Evaluating *in vitro* cytotoxic effects of *Artemisia afra* and *Artemisia annua* infusions against selected lung cancer cell lines. S Afr J Bot 150:404–411. https://doi.org/10.1016/j.sajb.2022.07.028

Van Wyk BE, Van Oudtshoorn B, Gericke N (1997) Medicinal plants of South Africa. 1st ed. Pretoria: Briza Publications. ISBN: 978-1-875093-37-3

Venables L, Koekemoer TC, Van de Venter M, Goosen ED (2015) Isoalantolactone, a sesquiterpene lactone from *Artemisia afra* Jacq. Ex Willd and its *in vitro* mechanism of induced cell death in HeLa cells. S Afr J Bot 103:216–221. https://doi.org/10.1016/j.sajb.2015.08.016

Viladomat F, Bastida J, Codina C, Nair JJ, Campbell WE (1997) Alkaloids of the South African Amaryllidaceae. Nat Prod Comm 1:131–171. https://doi.org/10.1177/1934578X1300800938

Vogel D, Loots E, Oladimeji O, Gouws C, Van der Kooy F (2023) The anti-neoplastic activity of *Artemisia afra* in breast cancer cell lines. S Afr J Bot 157:115–121. https://doi.org/10.1016/j.sajb.2023.03.049

Van der Walt L (2004) *Artemisia afra.* PlantZAfrica.com. https://pza.sanbi.org/artemisia-afra. Accessed 25 March 2024

Wassel GM, Rizk AM, Adbel-Bary EF (1972) Phytochemical investigation of *Prosopis juliflora* D.C.I. flavonoids and free sugars. Plant Food Hum Nutr 22:119–121. https://doi.org/10.1007/BF01099743

Watt JM, Breyer-Brandwijk MG (1962) The medicinal and poisonous plants of Southern and Eastern Africa, 2nd edn. E. & S. Livingston Ltd., Edinburg and London

Wildman WC (1960) Alkaloids of the Amaryllidaveae. In: Manske RHF *The alkaloids: chemistry and physiology.* Maryland:National Heart Institute 290–409. https://doi.org/10.1016/S1876-0813(08)60178-5

Williams CA, Harborne JB, Mathew B (1988) A chemical appraisal via leaf flavonoids of Dahlgren's *Liliiflorae*. Phytochemitsry 27:2609–2629. https://doi.org/10.1016/0031-9422(88)87033-X

Zdero C, Bohlmann F (1989) Sesquiterpene lactones and other terpenes from *Geigeria* species. Phytochemistry 11:3105–3120. https://doi.org/10.1016/0031-9422(89)80289-4

Zugazagoitia J, Guedes C, Ponce S, Ferrer I, Molina-Pinelo S, Paz-Arez L (2016) Current challenges in cancer treatment. Clin Therap 38:1551–1566. https://doi.org/10.1016/j.clinthera.2016.03.026