PHYTOCHEMISTRY, MEDICINAL PROPERTIES, BIOACTIVE COMPOUNDS AND THERAPEUTIC POTENTIAL OF THE GENUS *COMBRETUM* (COMBRETACEAE)

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Contents

Summary

The genus *Combretum* (family Combretaceae) consists of approximately 370 species that are endemic throughout the tropical and subtropical regions of Africa and Asia. Different *Combretum* spp. are used as traditional medicine systems by multiple ethnic populations in the areas in which they grow. They are used for their antibacterial, antifungal, antimalarial, antiviral, antidiarrhoeal, analgesic, antioxidant, antiinflammatory and anticancer properties. Many species of this genus are beneficial

against several diseases and ailments. Despite the reported ethnopharmacological uses of numerous *Combretum* species, few studies have rigorously examined the species in this important genus for many of their medicinal properties/mechanisms. In contrast, the anticancer properties of the genus have been relatively well studied, with a number of important compounds identified and their mechanisms studied. In particular, several combretastatins (stilbenes) have been recognized as promising for the treatment of different cancers. Combretastatin A-4 is particularly interesting and is currently undergoing clinical trials for the treatment of several types of cancer. The genus is also known for its anti-infective properties, which may be at least partially due to the high tannin content, and is common to the genus. Since the complexities of tannins make them poor candidates for drug design, much of the interest in *Combretum* spp has been centered on their pharmacognostic and nutraceutical value, and (with some notable exceptions) they are often overlooked for drug discovery. Increases in the number of studies into the use of *Combretum* species as therapeutic agents has arisen over the 2010s, although considerable work is still required. This chapter summarises the recent research into the medicinal properties, phytochemistry and therapeutic mechanisms of *Combretum* species in order to point out to the various future areas of research relevant to the medicinal activities of this important genus.

1. Introduction

Plants have been used traditionally for their therapeutic properties for thousands of years and they remain the primary healthcare modality in many developing countries. Ayurvedic medicine is commonly practiced in India and surrounding countries. Indeed, approximately 85% of Indian citizens regularly use herbal medicine preparations to maintain their health and to treat a myriad of diseases (Kamboj, 2000). Similarly, Traditional Chinese Medicine (TCM) and several traditional African medicinal systems are important components of the health care in those regions. Traditional and herbal medicines are also commonly used in developed countries due to their availability and affordability and are attracting much recent attention as complementary and alternative therapies. Furthermore, many allopathic medicines used clinically are derived from traditional plant-based medicines or are semi-synthetic analogues of plant derived compounds. Indeed, approximately 25% of all prescription drugs currently used are plant derived and 75% of all newly developed anticancer drugs adopted for clinical use between 1981 and 2006 were derived from plant compounds (Newman and Cragg, 2007). A major focus of modern drug discovery involves isolating and characterising individual bioactive phytochemical components from traditionally used medicines and modifying those compounds to produce analogues with increased bioactivity/bioavailability. This approach has yielded many useful drugs including quinine (from *Cinchona* spp.), digoxin (from *Digitalis* spp.), and the commonly used anticancer drugs paclitaxel (from *Taxus brevifolia* Nutt.), vincristine and vinblastine (from *Vinca rosea*). Thus, bioactivity, mechanistic and phytochemistry evaluations of traditional medicines have the potential to provide many new drugs with enhanced efficacy and/or safety and much further work is required.

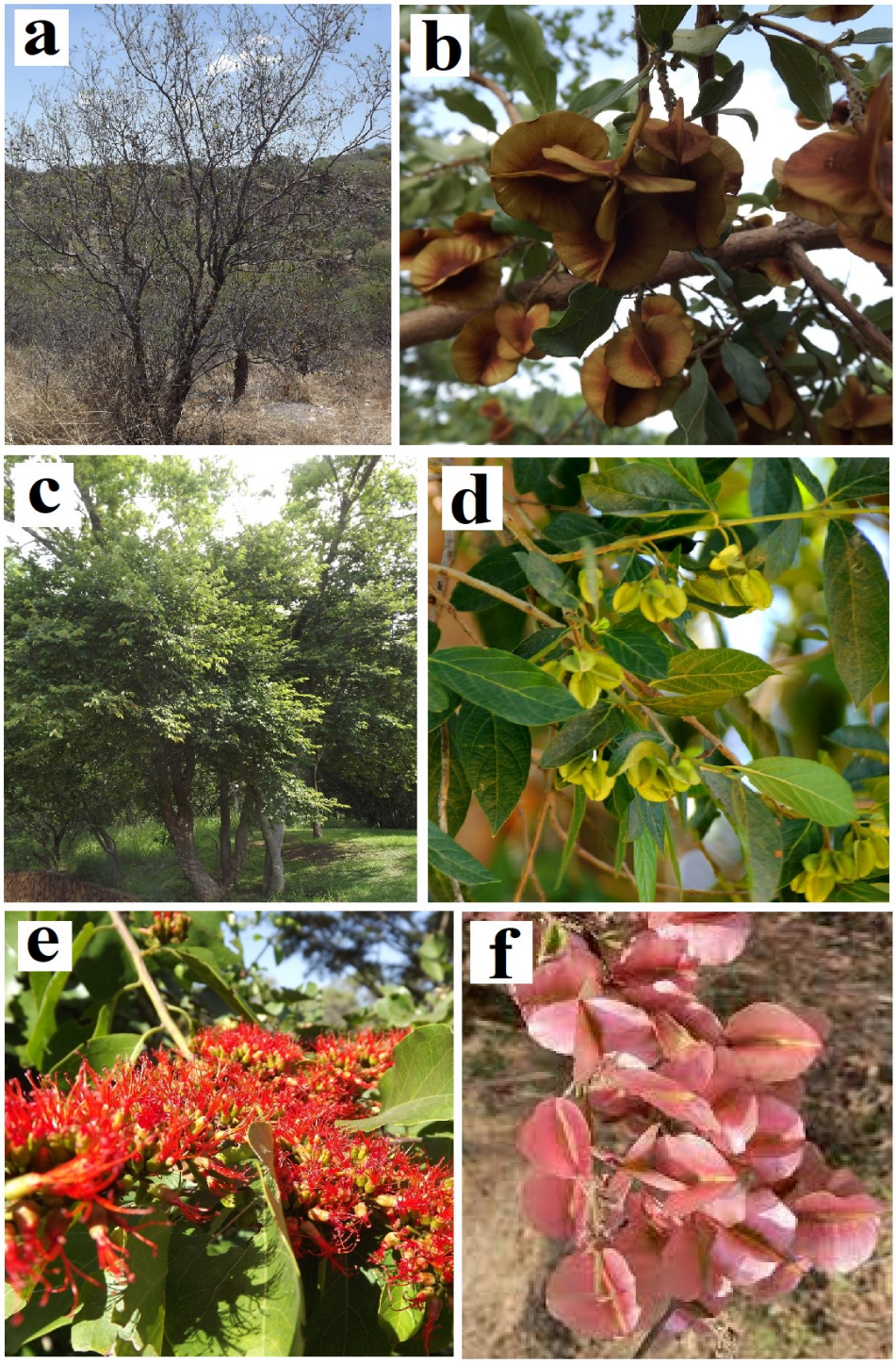

Figure 1: Some common *Combretum* spp. (a) and (b) *Combretum apiculatum* whole plant and fruit respectively; (c) and (d) *Combretum erythrophyllum* whole plant and fruit respectively; (e) and (f) *Combretum paniculatum* flowers and fruit respectively. All photographs were taken by Dr Ian Cock in South Africa between 2012 and 2019.

Combretum is the largest genus of family Combretaceae. The vast majority of *Combretum* (~300 species) are native to the African continent and are particularly prevalent in southern Africa where they are commonly known as bushwillows. Some

common *Combretum* spp. are shown in Figure 1. Five more species are native to Madagascar, with a further 25 native to tropical regions of Asia. Approximately 40 further species are native to tropical regions of the Americas. Many *Combretum* spp. have recorded uses in ethnomedicinal systems, particularly in southern African and Indian medicinal systems where they have been recorded as being used to treat pathogenic infections, diarrhoea, malaria, inflammation, cancer, diabetes, bleeding and digestive disorders (Khumalo et al, 2021; Cock et al, 2020a; Cock et al, 2019; de Morais Lima et al, 2012). The biology and phytochemistry of the southern African species have been well studied due to their usage in South African ethnomedicinal systems given their high antioxidant capacities. The identification of interesting compounds (particularly the promising anticancer compound combretstatin A-4) has generated substantial recent interest in southern African *Combretum* spp. Of those native to southern Africa, *Combretum caffrum* (Eckl. & Zeyh.) Kuntze*, Combretum erythrophyllum* (Burch.) Sond. and *Combretum molle* R.Br. ex G.Don are particularly well documented due to their varied uses in South African traditional medicine by a wide variety of groups including the Zulu, Xhosa, Sotho and other communities.

As with many other Combretaceae, the species in the genus *Combretum* are characterised by their high antioxidant capacities and their high levels of tannins (Roy et al, 2014). These characteristics are fortuitous and account for much of the traditional usage of *Combretum* spp. Indeed, consumption of high antioxidant diets is associated with a decreased incidence of chronic and degenerative diseases including cancer (Potter, 1997; Hertog et al., 1996), cardiovascular disease (Vita, 2005), neurological degenerative diseases (Youdim et al, 2002), diabetes and obesity (Tsuda et al, 2003). Therefore, the high antioxidant capacities inherent in *Combretum* spp. may have both preventative and curative activities against many diseases by reducing oxidative cellular damage. Similarly, the complexity and abundance of the tannin components in *Combretum* spp. preparations would also contribute to their anti-pathogenic (Rayan et al, 2015; Cock, 2015; Buzzini et al, 2008; Wolinsky and Sato, 1984; Hogg and Embery, 1982), anticancer and anti-inflammatory activities (Shalom and Cock, 2018; Cock, 2015; Wu-Yuan et al, 1988). In addition to the tannins, the stilbene contents of the *Combretum* spp. have generated much interest due to the therapeutic properties of the stilbenes. Combretstatin A-4 has especially been regarded as a future drug in cancer chemotherapy due to its potent activity against multiple cancers (Bhardwaj et al, 2010; Shen et al, 2010; Dark et al, 1997). This report aims to summarise recent research into the phytochemistry, medicinal properties and therapeutic mechanisms of *Combretum* spp. and thereby to highlight gaps in the literature and direct future research into this important genus.

2. Ethnopharmacology

As the vast majority of *Combretum* spp. are native to southern Africa, the ethnobotanical uses of those species have been extensively reported. South African *Combretum* plants have been used traditionally for various diseases and ailments such as snake and scorpion bites, mental issues, heart problems, fever, pain and microbial infections (Dawe et al, 2013). These plant species are prepared for herbal use as decoctions and hot water infusions, or may be mixed with foods. In some cases, fumes of burnt plant parts or the fumes from a hot water steam bath are inhaled for the

remedial benefits of its therapeutic compounds. Traditionally, *Combretum* spp. are used separately as medicines in most traditional southern African healing systems, although multiple species may be mixed or combined with other medical plants as herbal remedies against some ailments. Various *Combretum* species including *Combretum collinum* Fresen., *Combretum erythrophloeum* Gilg. & Ledermann ex Engl., *C. erthrophyllum, Combretum hereroense* Schinz., and *C. molle* were traditionally used to treat colds, cough, venereal diseases, infertility, diarrhoea, dysentery, sores and wounds (Cock et al, 2015; Eloff, 1999; Hutchings, 1996; Watt and Breyer-Brandwijk, 1962).

A recent ethnobotanical study of medicinal plants used by the traditional healers in Sesheke district, Western Province, Zambia also reported the use *C. hereroense, C. imberbe* Wawra, *C. mossambicense* (Klotzsch) Engl. and *C. apiculatum* Sond. in the management of sexually transmitted infections (Chinsembu, 2016). According to the World Health Organisation (WHO), up to 80% of the African populations rely on traditional medicinal systems for their primary health care. The leaves and roots are most frequently used and are often boiled in water or prepared as cold-water decoctions for the treatment and management of sexually transmitted infections including syphilis, gonorrhoea and chlamydia infections in men (Chinsembu, 2016). Medicinal plants are also used by rural farmers in the Eastern Cape region of South Africa.

Most information on the ethnobotanical usage of *Combretum* spp. concerns the use of African species in traditional African healing systems. The traditional use of *Combretum* spp. in other regions of the world has been less extensively reported, with few reports available. This is understandable, as most species of this genus occur in southern Africa. In Australia, *Combretum trifoliatum* Vent. was recorded for the first time in the northern region of Cape York Peninsula in the latter half of the 20th century (Clarkson et al, 1986). However, no ethnobotanical information is available on this *Combretum* spp. in Australia.

Table 1 summarize the current knowledge on the ethnobotanical uses of *Combretum* species as traditional medicines, whilst Table 2 summarize the studies that have examined and verified these therapeutic uses. Roots, leaves, barks and seeds of *Combretum aculeatum* Vent have been traditionally used for the treatment of sexually transmitted diseases, tuberculosis, leprosy, purgative and as a vermifuge (Hamad et al, 2019). However, no information is available about the formulation and method of application for this species. Similarly, leaves and roots of *C. erythrophyllum* are traditionally used for the treatment of leprosy and sexually transmitted diseases (Hutchings, 1996; Van Wyk et al, 2000). However, seeds and fruit decoctions of this plant are also used to facilitate birth and as an anthelmintic (Hutchings, 1996). Therapeutically, leaf extracts of this species have antibacterial activity against *P. aeruginosa, K. pneumoniae. S. aureus, E. faecalis* and *E. coli* (Eloff, 1999; Cock and Van Vuuren, 2020; Cock and Van Vuuren, 2015; Eldeen and Van Staden, 2008; Eldeen and Van Staden, 2007; Martini et al, 2004; Eloff, 1998a; Laurens et al, 1985). *Combretum kraussii* Hochst. (Mhlonga and Van Wyk, 2019) and *Combretum woodii* Deummer (Hutchings, 1996) are also used to treat urinary tract and bladder infections, as well as sexually transmitted diseases. Leaf infusions of *C. molle* are used to treat colds (York et al 2011; Cock and Van Vuuren, 2020). In addition, roots of this plant are also used for the treatment of hookworm infestations (Cock and van Vuuren, 2018).

Additionally, *Combretum vendae* A.A. van Wyk is traditionally used orally as a root bark decoction to treat optical problems (Suleiman et al, 2010).

Combretum bracteosum (Hochst.) Engl. & Diels leaf and root decoctions are used orally to treat convulsions and epilepsy (Ahmed et al, 2014; Risa et al, 2004). Additionally, leaf extracts of this species also have good growth inhibitory activity against ringworm causing fungal species, with minimum inhibitory concentration (MIC) values of 20-80 µg/mL (Masoko et al, 2007; Cock and Van Vuuren, 2020). Furthermore, extracts prepared from *C. caffrum*, *Combretum celastroides* Welw. ex M.A. Lawson, *C. collinum*, *Combretum edwardsii* Exell., *C. erythrophyllum*, *C. glutinosum* Perrot. ex DC, *C. hereroense*, *C. imberbe*, *C. kraussii*, *C. microphyllum* Klotzsch, *C. miossambicense*, *C. moggii* Exell., *C. molle*, *C. nelsonii* Dummer, *C. nigricans* Lepr., *C. padoides* Engl. & Diels, *C. paniculatum* Vent., *C. woodii* Dummer, *C. paniculatum* Vent., *C. petrophilum* Vent. and *C. zeyheri* Sond. showed good antimicrobial activity against ringworm and *Candida* spp. fungi (Table 2), but poor antibacterial activity against *P. aeruginosa* (Table 2).

Combretum hereroense, *C. kraussii*, *C. molle*, *C. mossambicense*, *C. psidioides* Welw., and *C. zeyheri* are used to treat pain and inflammation in several traditional healing systems (Table 1). Oral decoctions and infusions of barks, roots, leaves and fruit of these *Combretum* spp. are traditionally prepared to treat these ailments. Leaf extracts of *C. apiculattum*, *C. edwardsii*, *C. erythrophyllum*, *C. hereroense*, *C. imberbe*, *C. moggii*, *C. nelsonii*, *C. padoides*, *C. woodii*, and *C. petrophilum* were investigated *in vitro* and were reported to have promising anti-inflammatory activity via COX-1 inhibition (McGaw et al, 2001; Khumalo et al, 2021). Flower and stem extracts of *C. leprosum* Mart have noteworthy antinociceptive activity (Pietrovski et al, 2006; de Sousa Lira et al, 2002). Furthermore, a methanolic bark extract of *C. molle* inhibited inflammation by 62% in rats at a dose of 300 mg/kg after 1 hour exposure (Ponou et al, 2008). Acetone *C. zeyheri* leaf extracts were investigated for their effects on oxidative stress and for anti-inflammatory responses via determination of nitric oxide production in LPS-activated RAW 264.7 macrophages, and by studying their effects in 15-lipoxygenase (LOX) inhibitory assays (Dzoyem and Eloff, 2015). The results were noteworthy, with 96% NO inhibition noted at 25 µg/mL and >70% 15-LOX inhibition at 100 µg/mL extract concentrations.

Combretum racemosum P. Beauv, *C. molle* and *C. celastroides* subsp. *laxiflorum* Welw. are used traditionally to treat hypertension by southern African traditional healers (Manga et al, 2012; York et al 2011; Cock and Van Vuuren, 2020). However, experimental validation of these traditional uses is yet to be reported and further studies are required. *Combretum nigricans* seed extracts also have therapeutic cardiovascular effects, including anti-hypotensive activity in a cat model (Bamgbose et al, 1977). Roots and leaves of *C. molle*, *C. padoides* and *C. zeyheri* are used traditionally to treat malaria (Cock et al, 2019). Root bark decoctions of *C. padoides* are consumed orally for this purpose (Ahmed et al, 2014; Gathirwa et al, 2011; Nguta el al, 2010). Alternatively, *C. zeyheri* is combined with *Ochna pulchra* Hook., or as a component of a complex combination which includes *Burkea africana* Hook. and *Diospyros chamaethamnus* Mildbr. (Von Koenen, 1996; Cock and Van Vuuren, 2019). In contrast, *C. zeyheri* leaves and roots of are inhaled nightly using a steam bath for the same purpose.

Experimentally, only *C. microphyllum*, *C. molle*, *C. psidioides* and *C. zeyheri* were investigated against *Plasmodium falciparum* and showed IC_{50} values of 1-33 µg/mL, 108 µg/mL (Asres and Balcha, 1998; Attindehou et al, 2004; Gansané et al, 2010), 6-40 µg/mL (Gessler et al, 1994) and 15 µg/mL (Clarkson et al, 2004; Cock and van Vuuren, 2019), respectively.

Only *C. padoides* (Ahmed et al, 2014; Gathirwa et al, 2011; Nguta et al, 2010) and *C. murconatum* Schumach. & Thonn. (Spiegler et al, 2015) have recorded traditional uses in the management of wound healing. Additionally, oral consumption of *C. padoides* root bark decoction is used to treat conjunctivitis and diarrhoea (Ahmed et al, 2014; Gathirwa et al, 2011; Nguta et al, 2010). Oral treatment with a *C. murconatum* decoction is also used in helminth infestations (Cock and van Vuuren, 2018).

Several *Combretum* spp., including *C. apiculatum*, *C. erythrophyllum*, *C. leprosum*, *C. micraanthum* G. Don, *C. nigricans*, *C. padoides*, *C. psidioides* and *C. zeyheri* have been therapeutically investigated to justify their anticancer properties. Leaf and root bark extracts of *C. apiculatum* (Frhrquist et al, 2006; Wall et al, 1996) and ethanolic *C. erythrophyllum* root bark extracts (Wall et al, 1996) inhibit topoisomerase II *in vitro*. Furthermore, *C. apiculatum* extracts are cytotoxic to T24 bladder and MCF7 breast cancer cells, with an IC_{50} of 25 µg/mL. Similarly, *C. hereroense* bark and flower extracts are also cytotoxic against MCF7 breast cancer cells (Nopsiri et al, 2014). Interestingly, *C. leprosum* flower extracts had strong cytotoxic effects against MCF7 breast cancer cells, with IC_{50} values of 0.5-4 µg/mL (Viau et al, 2014). Leaf extracts of *C. micraanthum* and *C. nigricans* also show anticancer activity against HCT-15 colon cancer cells, U-373 astrocytoma cells, A549 and J82 urothelial cells, with IC_{50} values ~25 µg/mL and ~41 µg/mL respectively (Nopsiri et al, 2014; Fyhrquist et al, 2006; Simon et al, 2003). In comparison, *C. padoides, C. psidioides* and *C zeyheri* were also cytotoxic against multiple cancer cell lines including T24 bladder, HeLa cervical, MCF7 breast cancer cells, U-373 astrocytoma, HCT-15 colorectal, A549 and J82 urithelial cells, TK10 renal and UACC62 melanoma cells (Table 2) (Nopsiri et al, 2014; Fyhrquist et al, 2006; Simon et al, 2003; Fouché et al, 2008).

Extracts prepared from *C. decandrum* Roxb. (DC), *C. latifoliujm* DC, and *C. quadrangulare* Kurz., leaves were reported to have high antioxidant activity, with DPPH and ABTS radical scavenging activities of IC_{50} values of 63 µg/mL, 53-176 µg/mL and 68-155 µg/mL, respectively (Nopsiri et al, 2014; Pannangpetch et al, 2008). However, further studies are required to invesitage the antioxidant activity of other *Combretum* species. Leaf extracts of *C. glutinosum* Perrot. ex DC and *C. micraanthum* have antiviral activity against hepatitis B (IC_{50} = 100 mg/mL) and herpes 1 and 2 viruses at a concentration of 7.5 µg/mL (Pousset et al, 1993; Ferrea et al, 1993). Additionally, *C. molle* roots exhibit antiviral activity against HIV-1 reverse transcriptase (IC_{50} = 10-37 µg/mL) and therefore are promising anti-HIV-1 therapies (Bessong et al, 2005). Furthermore, bark and leaf extracts of *C. molle* have good antiprotozoan activity against *Trypanosoma brucei* at IC_{50} values ranging from 2-10 µg/mL (Asres et al, 2001; Bizimana et al, 2006). *Combretum quadrangulare* leaf extracts also have significant antiviral activity against several HIV-1 enzymes, with IC_{50} values in the range of 2.5-2.9 µg/mL (Tewtrakul et al, 2003). These extracts also had

significant antiprotozoan activity against *Trypanosoma cruzi* epimastigotes, with an IC_{50} value of 6 μg/mL (Kiuchi et al, 2002).

Extracts prepared from *C. decandrum* and *C. micraanthum* leaves have noteworthy antidiabetic activity in streptozotocin-induced diabetes in rats at 0.75 g/kg and 100-400 mg/kg, respectively (Pannangpetch et al, 2008; Chika and Bello, 2010). Interestingly, despite this reported activity, the traditional use of these species to treat diabetes has not been documented. However, the anti-diabetic activity of this species indicates that other *Combretum* spp. may have similar therapeutic properties and thus the investigation into the antidiabetic effects of other *Combretum* spp. is required. Table 1 list the use of parts of Combretum spp. in traditional healing systems and methods of preparation of medicines. Table 2 list Combretum spp. that have been screened for therapeutic properties.

Species	Common/ traditional name	Indication	Part used	Preparation method	Reference(s)
Combretum aculeatum Vent	Unknown	Purgative	Roots	Not specified	Hamad et al, 2019
		Vermifuge	Roots	Not specified	
		Leprosy	Bark, leaves, seeds	Not specified	
		Tuberculosis	Bark, leaves, seeds	Not specified	
		Treatment of sexually transmitted diseases	Roots	Not specified	
Combretum bracteosum (Hochst.) Engl. & Diels	Hiccup nut (English), hikklimop (Afrikaans), uQotha (Xhosa)	Epilepsy and convulsions	Leaves and roots	A decoction was consumed orally	Ahmed et al, 2014; Risa et al, 2004
Combretum celastroides subsp. *laxiflorum* Welw	Unknown	Hypertension	Leaves	A decoction was consumed orally	Manga et al, 2012
Combretum erythrophyllum (Burch.) Sond.	River bushwillow (English), riviervaderlands wilg, rooiblaar, rooiblad (Afrikaans), umbondwe, umdubu-wehlandze,	Sexually transmitted diseases	Leaves	Not specified	Hutchings, 1996; Van Wyk et al, 2000
		Treat leprosy	Root	Not specified	Hutchings, 1996
		Anthelmintic	Seeds, fruit	A decoction was consumed orally	Hutchings, 1996

	umhlalavane (Zulu), umdubu (Xhosa), miavana, modubo (Southern Sotho), modibo (Northern Sotho), mugavhi, mugwiti, muvuvhu (Venda)	Facilitate birth	Seeds, fruit	A decoction was consumed orally	Hutchings, 1996
Combretum hereroense Shinz	Russet bushwillow, mouse-eared combretum (English), kierieklapper (Afrikaans), mokabi (Sotho), mugavhi (Venda), umhlalavane (Zulu)	Inflammation and headaches	Fruit	A fruit decoction was consumed orally	Motlhanka and Nthoiwa 2013; Khumalo et al,2021
Combretum kraussii Hochst.	Umduba, Umdubu, omhlophe, Umdubo, wamanzi (Zulu)	Inflammation and pain	Root	Infusions were used to soak the affected body part	Van Wyk, 2011; Khumalo et al, 2021
		Urinary tract and bladder infections	Not specified	Preparation and application not specified.	Mhlonga and Van Wyk, 2019
Combretum molle R.Br. ex G.Don	Isibondwe, Umbonda, Umbondwe (isiZulu)	Inflammation and pain	Bark and roots	Powdered roots are used as an analgesic to relieve general body pains and internal sharp body pains, bark infusion is to treat lower back pains	Mabogo 1990; Hutchings, 1996; Mhlongo 2019; Khumalo et al. 2021
		Used to treat colds	Leaves	An infusion is drunk to treat colds.	York et al 2011; Cock and Van Vuuren, 2020c

		Used to treat tuberculosis	Bark	Preparation and application not specified.	McGaw et al, 2008; Cock and Van Vuuren, 2020b
		Used to treat malaria	Roots and leaves	Preparation and application not specified.	Prozesky et al, 2001; Cock and Van Vuuren, 2019
		Hookworm	Roots and Leaves	Preparation and application not specified.	Watt and Breyer-randwijk, 1962; Von Koenen, 1966; Cock and van Vuuren (2018)
		Cardiovascular disease and hypertension	Not specified	Not specified	Mhlonga and Van Wyk, 2019
Combretum mossambicense (Klotzsch) Engl.	Knobbly creeper (English), knoppiesklimop (Afrikaans)	Inflammation and swelling	Not specified	Steam from the plant is inhaled for facial swellings and used for eye inflammation	Von Koenen, 2001; Khumalo et al in preparation
Combretum murconatum Schumach. & Thonn.	Unknown	Wound healing	Not specified	A decoction was consumed orally	Spiegler et al, 2015
		Helminth infestations	Not specified		
Combretum padoides Engl. & Diels.	Thicket bushwillow (English)	Conjunctivitis	Leaves, roots	A root bark decoction was consumed orally	Ahmed et al, 2014; Gathirwa et al, 2011; Nguta et al, 2010
		Diarrhoea			
		Malaria			
		Wounds			
Combretum platypetalum Welw. Ex M.A. Lawson	Unknown	Used to treat pneumoniae	Roots	A root bark decoction was consumed orally	Von Koenen, 2001; Cock and Van Vuuren, 2020b
Combretum psidioides Welw.	Mupupu (Gci), ghupupu (Mbu)	Inflammation and swelling	Roots	Used for pain and inflammation (preparation and mode of administration are not specified)	Von Koenen, 2001; Khumalo et al, 2021

Combretum racemosum P. Beauv	Unknown	Hypertension	Leaves, root bark	Preparation and administration not specified	Manga et al, 2012
Combretum vendae A.A. van Wyk	Unknown	Leprosy	Leaves	A root bark decoction was consumed orally	Watt and Breyer-Brandwijk, 1962; Suleiman etal, 2010
		Optical problems		A root bark decoction was consumed orally	
Combretum woodii Deummer	Large leaved forest bushwillow	Abdominal pains	Leaves	A decoction was consumed orally	Hutchings, 1996
		Sexually transmitted diseases			
Combretum zeyheri Sond.	Large-fruited bushwillow, Zeyher's bushwillow (English), raasblaar, fluisterboom (Afrikaans), moduba-tshipi (Pedi), umbondwe wasembudwini (Zulu), mufhatelathundu (Venda)	Used to treat malaria	Roots, leaves	Combine with *Ochna pulchra* or a multiple combination including *Burkea africana* and *Diospyros chamaethamnus* where roots and leaves are used in steam bath nightly	Von Koenen, 1996; Cock and Van Vuuren, 2019
		Pain and inflammation	Roots, stem bark	Used for pain and inflammation (preparation and mode of administration are not specified)	Dzoyem and Eloff, 2015; Khumalo et al, 2021

Table 1. The use of Combretum spp. in traditional healing systems, including the indication, plant part used and how the medicine was traditionally prepared.

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Lall N, Meyer JJ. (1999) *In vitro* inhibition of drug-resistant and drug-sensitive strains of *Mycobacterium tuberculosis* by ethnobotanically selected South African plants. *Journal of Ethnopharmacology*. 1999 Sep 1;66(3):347-54. [*C. molle* extracts found to inhibit bacterial and mycobacterial growth]

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Mangoyi R, Mafukidze W, Marobela K, Mukanganyama S. (2012) Antifungal activities and preliminary phytochemical investigation of *Combretum* species from Zimbabwe. *Microbial and Biochemical Technology*. 2012;4:037-44. [Identified a spectrum of phytochemicals in selected *Combretum* species]

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Alternative Medicine. 2015 Dec;15(1):1-1. [Identified a compound purified from *C. zeyheri* as an antifungal agent]

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Martini N, Eloff JN. (1998) The preliminary isolation of several antibacterial compounds from *Combretum erythrophyllum* (Combretaceae). *Journal of Ethnopharmacology*. 1998 Oct 1;62(3):255-63. [Identified *C. erythrophyllum* leaf extracts as having antibacterial activities]

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Masoko P, Picard J, Eloff JN. (2007) The antifungal activity of twenty-four southern African *Combretum* species (Combretaceae). *South African Journal of Botany*. 2007 Apr 1;73(2):173-83. [Identified three *Combretum* species as having antifungal properties]

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Mogashoa MM, Masoko P, Eloff JN. (2019) Different *Combretum molle* (Combretaceae) leaf extracts contain several different antifungal and antibacterial compounds. *South African Journal of Botany*. 2019 Nov 1;126:322-7. [*C. molle* leaf extracts found to inhibit plant pathogenic fungal species]

Mohieldin EA, Muddathir AM, Mitsunaga T. (2017) Inhibitory activities of selected Sudanese medicinal plants on *Porphyromonas gingivalis* and matrix metalloproteinase-9 and isolation of bioactive compounds from *Combretum hartmannianum* (Schweinf) bark. *BMC Complementary and Alternative*

Medicine. 2017 Dec;17(1):1-1. [*P. gingavalis* shown to be inhibited by compounds isolated from *C. hartmannianum* extracts]

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Morales M, Ros Barcelo A, Pedreno MA. (2000) Plant stilbenes: Recent advances in their chemistry and biology. *Advances in Plant Physiology*. 2000;3:39-70. [Discussed pathways in stilbene synthesis by plants]

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Mulaw T, Wubetu M, Dessie B, Demeke G, Molla Y. (2019) Evaluation of antimalarial activity of the 80% methanolic stem bark extract of *Combretum molle* against *Plasmodium berghei* in mice. *Journal of Evidence-Based Integrative Medicine*. 2019 Nov 29;24:2515690X19890866. [*C. molle* bark extract shown to significantly suppress *Plasmodium berghei* growth]

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Natachit K, Santiarvorn D, Khantawa B. (2006) Antibacterial activity of the seeds of *Combretum quadrangulare* Kurz (Combretaceae). *CMU. Journal*. 2006;5(3):333. [Flavanoid glycosides were found in *C. quadrangulare*]

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Netshiluvhi TR. (2012) Influence of environmental parameters on efficacy of herbal medicines. Doctoral Thesis, University of Pretoria, 2012. [Acetone extracts prepared from *C. collinum* have been shown to inhibit *S. aureus* growth]

Newman DJ, Cragg GM. (2007) Natural products as sources of new drugs over the last 25 years. *Journal of Natural Products*. 2007 Mar 23;70(3):461-77. [Discussed the sources of plant-derived drugs]

Nguta JM, Mbaria JM, Gakuya DW, Gathumbi PK, Kiama SG. (2010) Antimalarial herbal remedies of Msambweni, Kenya. *Journal of Ethnopharmacology*. 2010 Mar 24;128(2):424-32. [Showed that oral consumption of *C. padoides* root bark decoction is used to treat various diseases]

Nishimura S, Manabe I, Nagasaki M, Eto K, Yamashita H, Ohsugi M, Otsu M, Hara K, Ueki K, Sugiura S, Yoshimura K. (2009) CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. *Nature Medicine*. 2009 Aug;15(8):914-20. [Discuss how inflammation can lead to more chronic illnesses]

Njume C, Afolayan AJ, Samie A, Ndip RN. (2011) Inhibitory and bactericidal potential of crude acetone extracts of *Combretum molle* (Combretaceae) on drug-resistant strains of *Helicobacter pylori*. *Journal of Health, Population, and Nutrition*. 2011 Oct;29(5):438. [Showed *C. molle* extracts to have antibacterial activity but not towards *H. pylori*]

Nopsiri W, Chansakaow S, Putiyanan S, Natakankitkul S, Nantachit K, Khantawa B, Santiarworn D. (2015) Chemical constituents and antibacterial activity of volatile oils of *Combretum latifolium* Bl. and *C. quadrangulare* Kurz Leaves. *Chiang Mai University Journal of Natural Sciences*. 2015;14:245-56. [Showed mild inhibition of bacterial growth with volatile oils from *C. quadrangulare* or *C. latifolium* leaves]

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Journal of Natural Products and Resources (IJNPR) [Formerly *Natural Product Radiance (NPR)*]. 2020 Aug 5;11(1):38-45. [Demonstrated *C. punctatum* var *squamosum* ethyl acetate leaf extracts as significantly reducing inflammation in rats]

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Biographical Sketches

Dr Ian Cock leads a research team in the Environmental Futures Research Institute and the School of Natural Sciences at Griffith University, Australia. His research involves bioactivity and phytochemical studies into a variety of plant species of both Australian and international origin including *Aloe vera*, South Asian and South American tropical fruits, as well as Australia plants including *Terminalia ferdinandiana* (Kakadu plum), *Tasmannia lanceolata*, *Scaevola spinescens*, *Pittosporum phylliraeoides*, Australian *Acacias, Syzygiums, Petalostigmas* and *Xanthorrhoea johnsonii* (grass trees). This range of projects has resulted in nearly 250 scientific publications in a variety of international peer reviewed journals. Dr Cock is also active in the administration and editorial aspects of scientific publication. He is currently on the editorial boards of 9 international peer reviewed journals. Of these, he is the editor in chief and foundation editor of the journal Pharmacognosy Communications.

Dr Matthew Cheesman is a molecular biologist and biochemist who is interested in natural product discovery and the development of new antibacterial treatment therapies. His research focus is on plants as sources of new medicines for the treatment of multi-drug resistant infections. His work has resulted in nearly 40 scientific publications in a variety of international peer reviewed journals.

Mr Gagan Tiwana completed a Master of Pharmacy project on the medicinal properties of plants. He is completing a PhD in the area of traditional medicines in order to explore their potential in treating infectious diseases.