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Combretum species around Africa as alternative medicine: Ethnopharmacological and ethnobotanical importance

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ABSTRACT

Herbal medicine is a form of medicine that has been extensively exploited in traditional medicine, and its therapeutic potential is accepted. *Combretum* is one of the most frequently happening genera in the African and Asia tropical and subtropical areas; some are widely used in African herbal medicine due to their ethnopharmacological properties. Numerous species of this plant have been used and expended owing to high pharmaco-constituents following their phytochemical screening and evaluations. The recent incidence of multidrug-resistant strains and reduced receptiveness to antibiotics has raised serious anxiety in health delivery and the need for an urgent search for new antibiotics mediators from nature. A countless number of natural substances have resulted from the *Combretum* species as medicine and are utilized traditionally for the management of bacteriological infection. The plants have received comprehensive documentation as a good cradle of natural constituents that can be categorized into four groups following their biosynthetic source: alkaloids, terpenoids, polyketides, and phenylpropanoids. The study deals with the ethnobotanical and pharmacological significance of the *Combretum* species for treating numerous ailments and diseases.

INTRODUCTION

Communicable ailments are significant sources of morbidity and death universally, notably in developing countries, accounting for about 50% of diseases in countries with low healthcare facilities and as much as 20% of mortality rates in industrialized countries (Khalil *et al.*, 2020; Motsumi *et al.*, 2020; Mtunzi *et al.*, 2017a; Ntshanka *et al.*, 2020). Despite the high level of innovation and antibiotic application in microbiology, the intermittent occurrences of epidemics caused by drug-resistant microbes and the emergence of unknown disease-causing microorganisms pose a significant threat to healthcare (Abubakar, 2010; Nguedia and Shey, 2014; Silber *et al.*, 2016).

The development of resistant strains to some antibiotics has complicated the management of infectious diseases, given that drugs are only effective against one-third of existing ailments (Fankam *et al.*, 2015; Sahu *et al.*, 2014). Microbial drug resistance became persistent because of drug abuse and misuse of antibiotics. Most drugs are ineffective against diseases for which they had previously been misused. This results in resistant pathogens becoming virulent, increasing the risk of complications and death (Fankam *et al.*, 2015; Nguedia and Shey, 2014; Sampedro *et al.*, 2009). Most drugs are discovered from biological natural resources, and natural yields from microbes have been the major cradle of

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antibiotic delivery. With the cumulative approval of herbal medicine as a substitute form of healthcare, the selection of herbal plants for bioactive constituents has become a very imperative aspect of the health system because they serve as a favorable cradle of innovative antibiotic exemplars (Khan *et al.*, 2022; Sabo and Knezevic, 2019; Serralheiro *et al.*, 2020). Antibiotics derived from fungi or living organisms are produced industrially using a fermentative process (Alfadil *et al.*, 2014; Silber *et al.*, 2016; Wright *et al.*, 2014).

The predominance of other diseases like hematological and autoimmune disorders, human immunodeficiency virus (HIV) infection, cancer, and important immune system dysfunction may cause symbiotic microbes to change to pathogens under definite circumstances, typically called opportunistic contamination. Opportunistic pathogens consist of fungi, viruses, protozoa, and bacteria, taking advantage of immunocompromised patients and displaying new health challenges worldwide. Opportunistic diseases involve diminishing host defenses, occurring because of genetic deficiencies, introduction to antibiotics, and immunosuppressive substances or due to communicable diseases possessing immunosuppressive properties (Nagata *et al.*, 2011; Ntshanka *et al.*, 2020; Ryan and Ray, 2004; Yang *et al.*, 2013).

Some chemotherapeutic mediators presently used are noxious with accompanying antagonistic side effects. Hence, there is a general necessity for novel chemotherapeutic mediators against several disease pathoaetiologies that are exceedingly resourceful, have low toxicity, and exhibit minor ecofriendly impacts. Herbal medications have various traditional claims, such as managing infectious sources. Several extracts of plant species were established against hundreds of microbial strains via various *in vitro* models and some had good action pharmacological consequences (Bhat, 2014; Fankam *et al.*, 2015; Khumalo *et al.*, 2018; Luís *et al.*, 2016; Motsumi *et al.*, 2020; Nguedia and Shey, 2014). However, a limited number of these herbal plant extracts have been screened in animal or human studies to regulate safety and efficiency. Natural products and their byproducts characterize about 50% of all drugs in clinical use (Cragg and Newman, 2013; Fankam *et al.*, 2015; Khumalo *et al.*, 2018; Lahlou, 2013).

Natural products from natural cradles like plants, animals, and microorganisms, dated before human antiquity, perhaps thousands of years (Ji *et al.*, 2016; Khan, 2018). These products can be categorized into four diverse groups according to their biosynthetic derivation, polyketides, alkaloids, terpenoids, and phenylpropanoids (Bisht *et al.*, 2021; Guo, 2017), and continue to offer novel chemical structures with high levels of biological activity (Guo, 2017; Khan, 2018; Moloney, 2016). The mechanisms underlying many biological properties have been ascribed to numerous types of propolis, including antitumor, anti-inflammatory, wound healing, antioxidant, antimicrobial, and immunomodulatory activities (Shaikh *et al.*, 2016). Plants do produce potentially toxic substances aside production of beneficial phytochemicals; therefore, toxicity assays incorporation in the bioactivity evaluation of medicinal plants is very important in understanding their therapeutic effects (Alam *et al.*, 2018; Araújo *et al.*, 2013; Cundell, 2014; Luís *et al.*, 2016; Ntshanka *et al.*, 2020; Shah *et al.*, 2010; Verma, 2016). The Chinese traditional medicine community is the world's largest medicinal plant user is, with more than 5,000 plants and plant products registered in their pharmacopeia (Ji *et al.*, 2016).

Traditional medicine in South Africa supports using abundant plant species for the treatment or management as prophylaxis against several kinds of ailment (infectious and noninfectious) (Masoko *et al*., 2010, 2012; Mtunzi *et al.*, 2017a, 2017b; Street and Prinsloo, 2013). In South Africa, medicinal species are being traded for usage in local medicines since most are from ethnopharmacological guides (De Wet *et al.*, 2013; Mabona and Van Vuuren, 2013; Street and Prinsloo, 2013). The sustainable use and control of medicinal plants are of a significant contest to all shareholders. Parts of many medicinal plants, like the stem, bark, and roots, are being harvested and merchandized in an unmanageable routine that may lead to the augmented death of the tree that is the source of medication. Assessment and authentication of leaf extract bioactivity as a promising substitute for stem, roots, and bark use to afford a viable opportunity for safeguarding medicinal plants (De Wet *et al.*, 2013; Street and Prinsloo, 2013). Herbal medicine is the most significant medicine for most people on planet earth, specifically those who do not have access to modern and expensive drugs. Interestingly, it has formed the foundation of every medicine, the mother of all remedies in modern days. The exploitation of medicinal plants as herbal medicine alongside their curative perspective is well documented (Alam *et al.*, 2018; Bhat, 2014; Cundell, 2014; Motsumi *et al.*, 2020; Mtunzi *et al.*, 2017a, 2017b; Sabo and Knezevic, 2019; Street and Prinsloo, 2013). The World Health Organization estimates that populace about 80% residing in developing nations exclusively practice traditional medicine (Eloff, 1998; Motsumi *et al.*, 2020; Mtunzi *et al.*, 2017a).

Medicinal plant therapies have also been featured conspicuously in the ailments treatment of production and domestic animals, and ethnoveterinary therapeutic practices remain an imperative aspect of animal healthcare in unindustrialized countries (Ji *et al.*, 2016; Khan, 2018). *Combretum* species is featured conspicuously among the utilized medicinal plants in South African traditional medicine as agents for handling communicable diseases like diarrhea (*Combretum imberbe* Wawra*, Combretum vendee* A.E.van Wyk), malaria (*Combretum ghasalense*), stomach disorders (*Combretum molle* R. Br. ex G. Don.), and coughs [*C. molle* R. Br. ex G. Don.*, C. imberbe* Wawra*, Combretum erythrophyllum* (Burch.) Sond.] (Eloff *et al.*, 2008; Mtunzi *et al.*, 2017b; Ntshanka *et al.*, 2020). *Combretum erythrophyllum* is a member of the Combretaceae family, generally used for venereal disease management (Van Wyk and Gericke, 2000). Root parts are used as a laxative, while dried and pulverized gum is applied to blisters (Venter and Venter, 1996).

The roots and bark decoctions of *C. erythrophyllum* are utilized to treat cough and unproductiveness and as an aphrodisiac (Ahmed *et al.*, 2014; Mtunzi *et al.*, 2017b). The leaves are used to treat cough and stomach pains, while the seeds, which have been reported to be poisonous, are used to remove intestinal worms in dogs (Van Wyk *et al.*, 2009). *Combretum erythrophyllum* is commonly scattered in the Southern Africa region, most commonly found in South Africa along the coast in the Eastern Province, namely Zimbabwe, KwaZulu-Natal, Northern South Africa (Mpumalanga, Gauteng, Limpopo, and the eastern parts of Northwest regions), Swaziland, and Mozambique, and marginally into the eastern parts of Botswana (Silén *et al.*, 2023).

Martini *et al.* (2004a) isolated seven different flavonoids from leave extract *C. erythrophyllum* (Burch.) collected from a tree within the Pretoria National botanic gardens, South Africa, known to be antibacterial phenolic compounds which include four flavonols: rhamnocitrin **(1)**, rhamnazin **(2)**, 5,7,4′-trihydroxyflavonol (kaempferol) **(3)**, and 7,4′-dihydroxy-5,3′-dimethoxyflavonol (quercetin-5,3′-dimethylether) **(4)**; three flavones: 5,7,4′-trihydroxyfavone **(5)**, 5,4′-dihydroxy-7-methoxyflavone **(6),** and 5-hydroxy-7, 4′-dimethoxyflavone **(7)** (Fig. 1). All compounds possessed good activity against *Enterococcus faecalis* and *Vibrio cholera*, with the minimal inhibitory concentration (MIC) value <100 µg/ml. Rhamnocitrin and quercetin-5,3′-dimethyl ether inhibited *Shigella sonnei* and *Micrococcus luteus* with a MIC value of 25 µg/ml (Martini *et al.*, 2004a, 2004b; Mawoza and Ndove, 2015).

In literature, medicinal plants have presented interesting ethnopharmacological potentials as chemotherapeutic agents. The *Combretum* species has great prospects for the management of various infectious diseases (Eloff *et al.*, 2008) and will have a vital relevance with economic benefit to the perfumery industry (Alam *et al.*, 2018; Barrales-Cureno *et al.*, 2021; Crovadore *et al.*, 2012; Mohaddese, 2016; Sabo and Knezevic, 2019). Nevertheless, the tangible potential of *Combretum* has not been exploited to the fullest. Hence, this review has made an effort to present a comprehensive overview of the summary of earlier research data regarding ethnopharmacological properties, antimicrobial, antifungal, antioxidant, cytotoxicity activities, and other noteworthy effects of *Combretum* species as alternative medicine.

METHODS AND LITERATURE QUEST

An epistemological paradigm grounded in a qualitative research approach was utilized for this study. The study seeks to explain, clarify, define, elucidate, and expand more on the understanding of the ethnopharmacological potentials of medicinal plants concerning *Combretum* species as chemotherapeutic agents for drug discovery.

Available reports and references on the medicinal plant species were accessed from published scientific peer-reviewed journals, books, short communications, reports from national, regional, and international organizations and institutions, theses, conference papers, and other materials. International online databases, including ISI Web of Science, SCOPUS, EBSCO, MEDLINE (National Library of Medicine), chemical abstracts service, Science Direct, SCIMAGO, ProQuest, EMBASE, and Google Scholar, were utilized for literature search using precise search terms. Selected keywords were used but not limited to Combretum species, ethnopharmacological promises, properties of the Combretum genus, phytochemicals, pharmacological, antibiotics, medicinal plants, biological assays, chemical constituents, chemotherapeutic agents, traditional medicine, and traditional uses of medicinal plants of about 600 studies and research articles consulted, articles from 1970 to 2022.

Snowball sampling technique was used in this study, followed by content and semantic analysis of data collected from the literature for systematic documentation of the biological, pharmacological, and traditional uses of medicinal plants: *Combretum* species around Southern Africa region as alternative medicine.

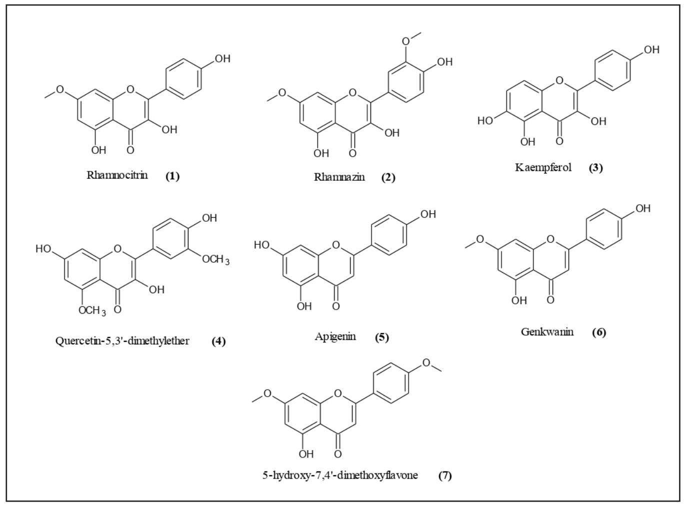

Figure 1. Chemical structures of flavonoids found in *Combretum erythrophyllum* (Martini *et al.*, 2004a).

RESULTS AND DISCUSSION

Combretaceae family

Combretaceae hosts more than 600 species (Komape *et al.*, 2014; Zhang *et al.*, 2020). *Combretum* is among the most frequently occurring genera of Combretaceae in tropical and subtropical areas of Africa and Asia. Due to their ethnopharmacological properties, some of these genera are widely used in African traditional medicine (Chukwujekwu and van Staden, 2016; Gumisiriza *et al.*, 2021). The different fragments of the *Combretum* species are broadly used to treat numerous diseases (Ares *et al.*, 2006; Eloff *et al.*, 2008; Mtunzi *et al.*, 2017b). The species of *Combretum*, generally known as the forest bushwillow tree (*C. kraussii* Hochst.), is medium to large in size and is found in the eastern part of South Africa, Swaziland, and Southern Mozambique (Chukwujekwu and van Staden, 2016; Zhang *et al.*, 2020). *Combretum kraussii* Hochst. is often used as herbal medicine to treat eye infections and wounds and serves as a blood tonic and an appetite stimulant. It can also act as antiseptic and antidiuretic agent, (Chukwujekwu and van Staden, 2016; Quattrocchi, 2012).

Therapeutic potentials of *Combretum* species

Combretum species as an antioxidant agent

An important development that produces free radicals in living systems, substances, and even in food is referred to as oxidation (Barku *et al.*, 2013). Oxidation is also the chemical reaction involving electron transfer from the electron-rich to the electron-deficient entity (Poljsak *et al.*, 2021). The electron-scarce molecule is labeled an oxidizer or oxidizing agent. Enzymes such as hydroperoxidase and catalase translate hydroperoxides and hydrogen peroxide (H_2O_2) to nonradical forms and perform natural antioxidants' role in the human body (Ofoedu *et al.*, 2021). The prescribed oxidation state refers to the postulated charge an atom has if all bonds to other atoms of different elements are completely ionic. It is generally epitomized by integers that can either be zero, positive, or negative (Norman and Pringle, 2022).

Free radicals are reactive species containing unpaired electron that attacks macromolecules, including protein, lipid, and DNA. Free radicals are the products of natural human metabolism. Varieties of endogenous free radicals destroying antioxidants exist in the body, while others are obtained from dietary sources like vegetables, fruits, and teas. At present, accessible synthetic antioxidants like gallic esters, butylated hydroxyl toluene, butylated hydroxyl anisole, and tertiary butylated hydroquinone are assumed to bring about or hasty negative health consequences (Mongalo *et al.*, 2012).

Antioxidants preclude oxidative impairment of cells, biomolecules, and reactive oxidative species oxidative species (ROS)-induced illnesses by reacting with free radicals, destroying free radicals, and chelating free catalytic metals (Pizzino *et al.*, 2017). Antioxidant consumption possesses numerous health benefits, including oxidative damage associated with free radical damage and its role in diseases (Ejidike *et al.*, 2019). Antioxidant nutrients, either endogenous or exogenous, natural or synthetic, can search for free radicals in the system and neutralize them before they further damage the body cells (Mandal *et al.*, 2022; Medrano-Macías *et al.*, 2022; Poljsak *et al.*, 2021). Antioxidants are important constituents in the human body that safeguards it from impairment caused by oxidative stress induced by free radicals (Ejidike and Ajibade, 2015; Poljsak *et al.*, 2021). There is emerging interest in the exploration of the antioxidant activities of secondary metabolites from medicinal species to compounds with greater potency and lower toxicities than the presently accessible synthetic ones (Medrano-Macías *et al.*, 2022; Motsumi *et al.*, 2020; Mtunzi *et al.*, 2017a; Ntshanka *et al.*, 2020; Poljsak *et al.*, 2021).

Recent epidemiological evaluations have revealed that many antioxidant compounds possess antibacterial, anticarcinogenic, anti-inflammatory, antiviral, antitumor, antiatherosclerotic, or antimutagenic activities to a bigger or smaller extent (Owen *et al.*, 2000; Verma, 2016). The antioxidant perspective of natural plant products is attributable to several compounds such as phenols and flavonoids, which have a distinct mechanism of action. Consequently, one antioxidant compound was sequestered from *C. erythrophyllum* and is 5-hydroxy-7,4′-dimethoxyflavone but exhibited the weakest activity (Martini *et al.* 2004a, 2004b). Oxidative stress is the inequality between the generation and eradication of ROS or reactive nitrogen species (RNS) in support of ROS (Ejidike and Ajibade, 2015; Poljsak *et al.*, 2021; Zhang *et al.*, 2009). Oxidative stress is proficient in triggering cells to lose their function and structure and ultimately cause cell dysfunction. ROS/RNS can be produced within the airway epithelial cells in answer to proinflammatory cytokines like tumor necrosis factor-alpha (TNF-α) (Ejidike and Ajibade, 2015; Lü *et al.*, 2010; Mandal *et al.*, 2022; Medrano-Macías *et al.*, 2022; Poljsak *et al.*, 2021).

ROS and RNS perform various functions, including regulation of gene expression (Mandal *et al.*, 2022) and stimulation of apoptosis (Huang and Zhou, 2021). The manufacture of ROS/RNS might have very detrimental effects and is neutralized by the antioxidant fortifications under standard circumstances in healthy people (Mandal *et al.*, 2022; Medrano-Macías *et al.*, 2022). Oxidative stress arises when there is a variation of balance in support of ROS/RNS and may happen in several situations, like in infection or malnutrition with deficient micronutrients to achieve the requirement for antioxidant defenses (Ejidike and Ajibade, 2015; Mandal *et al.*, 2022; Medrano-Macías *et al.*, 2022). It has been recognized that oxidative stress is among the chief contributory elements of various chronic and deteriorating ailments initiators comprising cancer, ischemic heart disease, atherosclerosis, diabetes mellitus, ageing, immunosuppressant, and neurodegenerative illnesses (Ejidike and Ajibade, 2015; Malekmohammad *et al.*, 2019; Poljsak *et al.*, 2021).

Combretum species as an antimicrobial and antiviral agent

Antimicrobial-resistant strains are the major causes of copious clinical problems (Fennel *et al.*, 2004; Gangoué-Piéboji *et al.*, 2009) and have increased the world's mortality rate (Ejidike and Ajibade, 2015; Motsumi *et al.*, 2020; Mtunzi *et al.*, 2017a, 2017b; Ntshanka *et al.*, 2020). The resistance built by pathogenic against antibiotics has brought about great interest and the quest for novel antimicrobial drugs/agents from nature (Bouzidi *et al.*, 2016; Dorman and Deans, 2000; Ejidike and Ajibade, 2015; Liouane *et al.*, 2010). The unethical usage of antibiotics has brought about their resistance to bacterial strains (Martini and Eloff, 1998). Plants are an imperative basis for the growth of new chemotherapeutic agents, given that they are made up of potentially useful constituents (Barku *et al.*, 2013). Since time immemorial, traditional plants have been used to prepare drugs, thus acting as a good source of medicine. Moreover, *Combretum* species have been shown to exhibit potential activities as antibacterial and antiviral agents (Adamu *et al.*, 2005; Filho *et al.*, 2015; Fyhrquist *et al.*, 2006; Katerere *et al.*, 2003; Maregesi *et al.*, 2007; Martini *et al*., 2004a, 2004b; Martini and Eloff, 1998; Masika and Afolayan, 2002; Masoko *et al*., 2007, 2010; Mawoza and Ndove, 2015; McGaw *et al.*, 2000; Ntshanka *et al.*, 2020; Olukoya *et al.*, 1993).

Different components of the *Combretum* plants have been utilized in the native system of medicine for the management of several human ailments ranging from ulcers, wounds, cholera, and snakebite to abdominal disorders (Begum *et al.*, 2002; Maregesi *et al.*, 2007; Masoko *et al.*, 2010; Mawoza and Ndove, 2015). The leaves, stems, roots, and flower parts of *Combretum* species have been used traditionally for the treatment of neuralgia, throat contagions, wounds, eruptions, and a varied range of skin diseases like rashes, ringworm, and ulcers (Eloff *et al.*, 2008; Masoko *et al*., 2007, 2010); treatment of related bacterial infections and diseases including pneumonia, chest infections, syphilis, diarrhea, coughs, and colds (Ahmed, 2012; Ahmed *et al.*, 2014; Dawe *et al.*, 2013; Fyhrquist *et al.*, 2006; Gathirwa *et al.*, 2011; Komape *et al.*, 2014; McGaw *et al.*, 2001; Ntshanka *et al.*, 2020); treatment of digestive infections, bleeding, and throat contagions (Dimitrova *et al.*, 2015; Hsouna and Hamdi, 2012); and also menopausal and menstrual complications, breast congestion, cellulite, and fluid retention (Pietrovski *et al.*, 2006; Saraswathi *et al.*, 2011). The leaf extracts have also been reported to treat childhood diseases like measles, chickenpox, and mumps (Brendler and Van Wyk, 2008). The following species have prominently featured as agents for treating contagious diseases: *C. imberbe, C. vendee* against diarrhea; *C. ghasalense* Engl. & Diels against malaria;

Table 1. Antimicrobial activities and uses of constitutes sequestered from the Combretum species in traditional medicine.

Combretum species	Common name	Ethnobotanical use	Biological activity	Bioactive compounds isolated
Combretum adenogonium Steud. ex A. Rich.	Four-leaved bushwillow	Leaves and stems are used for anti-inflammatory, hepatitis, arterial hypertension, and urinary infection. Aqueous stem bark powder is taken as an antiabortion solution. A decoction of the roots is used as a bath for children with convulsions. Plant parts are utilized for the management of cough, leprosy and snakebite, diarrhea, malaria, aphrodisiac, syphilis, long-lasting wounds, poisoned wounds, and fungal infection of the scalp (Batawila *et al.*, 2005; Fyhrquist *et al.*, 2006)	Methanolic extract of the stem barks exhibited *Clostridium chauvoei* (Jakari strain) neuraminidase activity inhibition at 100–1,000 µg/ml with an estimated LC_{50} value of 150 µg/ml (Useh *et al.*, 2004). Extracts from the root, leaf, and stem bark have the potential as antibacterial, antifungal, and antiproliferative agents (Fyhrquist *et al.*, 2006; Maregesi *et al.*, 2007). Ethanolic extracts of root, leaf, and stem bark have displayed antibacterial by microdilution methods, an anti-HIV-1 protease with LC_{50} value of 24.7 µg/ml and 26.5 µg/ml for root and stem bark extracts, respectively, and cytotoxic activities using brine shrimp's lethality assay (Mushi *et al.*, 2012)	Two phytosterols: stigmasterol and β-sitosterol (Maima *et al.*, 2008). 2,3,8-Trihydroxy-4,6-dimethoxy-9,10-dihydrophenanthrene (1β), and 2,3,8-trihydroxy-4,6-dimethoxyphenanthrene (1α) (Mushi *et al.*, 2015).
Combretum albopunctatum Suesseng (Ciliatipetala Engl. & Diels)	Thicket-forming shrub	Hexane, acetone, methanol, and dichloromethane leaf extracts possess antibacterial properties and antioxidant activities. Also, they are used in the wound healing process (Masoko and Eloff, 2007).	Antioxidant activities were observed for acetone and methanol extracts via qualitative DPPH assay on TLC (Masoko and Eloff, 2007). *In vitro* antifungal action with mean MIC values of 0.7 mg/ml on fungi strains. LC_{50} value on Vero kidney cells (monkey) by MTT assay was 102.9 µg/ml (Masoko *et al.*, 2010).	Phenolic compounds, namely, three (3)-flavonoids and two (2)- cyclobutane chalcone dimers: rel-1β-(4,6-dihydroxy-2-methoxy)-benzoyl-rel-2α-(2,6-dimethoxy-4-hydroxy)-benzoyl-rel-(3β,4α)-diphenylcyclobutane, rel-(1α,2β)-Di-(2,6-dimethoxy-4-hydroxy)-benzoyl-rel-(3α,4β)-diphenylcyclobutane, 5-Hydroxy-7-methoxyflavanone (alpinetin), 5,7-dihydroxyflavanone (pinocembrin), 4′,6′-dihydroxy-2′-methoxychalcone (cardamomin) (Katerere *et al.*, 2004).
Combretum apiculatum Sond. *ssp. apiculatum*	Red bushwillow	Aqueous roots are squashed and the juice is ingested for the management of snakebite. Methanol, hexane, ethanol, and aqueous leave extracts are used as preventives for abdominal disorders, while the stem bark serves for conjunctivitis (Aderogba *et al.*, 2012; Fyhrquist *et al.*, 2006; Katerere *et al.*, 2012; McGaw *et al.*, 2000; Olukoya *et al.*, 1993).	A strong antioxidant activities was demonstrated by Kaempferol and Quercetin and had with EC_{50} values of 47.36 ± 0.03 and 11.81 ± 85 µM respectively. Water extract by Microdilution assay revealed that *Staphylococcus aureus* and *Bacillus subtilis* possessed MIC = 0.39 mg/ml (Olukoya *et al.*, 1993). Methanol extracts of the leaves exhibited antioxidant activity, namely, spraying TLC chromatograms method and cytotoxicity activities on Vero kidney cells by the MTT assay (Aderogba *et al.*, 2012)	Flavokawain, alpenitin, and pinocembrin (Katerere *et al.*, 2012), cardamomin, pinocembrin, quercetin, and kaempferol (Aderogba *et al.*, 2012; Kgatle, 2007). 9,10-Dihydro-3,6,7-trimethoxy-2,5-phenanthrenediol (Letcher and Nhamo, 1971). 5-Hydroxy-3,4′-dimethoxybibenzyl; 4′,5-dihydroxy-3,4-dimethoxybibenzyl; 4,4′-dihydroxy-3,5-dimethoxybibenzyl; 4′-hydroxy-3,4,5-trimethoxybibenzyl (Katerere *et al.*, 2012).
Combretum bracteatum (Laws.) Engl. & Diels	Hiccup-nut	Water and ethanol leave and stem extracts have been used to treat earache, headache, fever, toothache, backache, and menstrual pains (Eloff, 1998; Olukoya *et al.*, 1993).	Water extracts of dried stems exhibited antimicrobial activity with a zone of inhibition value of 5–9 mm at 0.33 g/ml (Eloff, 1998).	Nigaichigoside F1; *β*-D-glucopyranosyl-3*β*,19*α*-dihydroxy-2-oxo-urs-12-en-28-oate; Chebuloside II; *β*-D-glucopyranosyl 2*α*,3*β*,6*β*-trihydroxyolean-12-en-28-oate; 1,2-di-*O*-*α*-linolenoyl-3-*O*-*β*-*D*-galactopyranosyl-sn-glycerol; 1,2-di-*O*-*α*-linolenoyl-3-*O*-[*α*-*D*-galactopyranosyl-(16)-*O*-*β*-D-galactopyranosyl]-sn-glycerol (Ntchatcho *et al.*, 2009).

Continued

Combretum species	Common name	Ethnobotanical use	Biological activity	Bioactive compounds isolated
Combretum caffrum (Eckl. & Zeyh.) Kuntze	Eastern Cape bushwillow	Alcohol and aqueous bark, leaf, and stem extracts are used as an all-purpose tonic for the manufacture of general well-being; roots decoctions are included in the bath water before bedtime for the treatment of body pains (Masika and Afolayan, 2002; Masoko and Eloff, 2007; Masoko *et al.*, 2007; Pettit *et al.*, 1989).	The methanol extract was active against gram-negative bacteria, while acetone, methanol, hexane, and stem-water fractions and bark exhibited antimicrobial activity against gram (+ve) bacteria and a few fungal pathogens (Masika and Afolayan, 2002). Tetrachloromethane, trichloromethane, and dichloromethane fractions of dried, stem, fruit, leaf, twig, and methyl chloride root extract have exhibited *in vitro* antitumor activity against murine-P388 lymphocytic leukemia; immature astrocytoma 224c glioma cell (Pettit *et al.*, 1995, 1999).	Combretastatins: A-1, A-2, A-3, A-4, B-1, B-2, B-3, and B-4 were isolated from the wood (Pettit *et al.*, 1989, 1995, 1999).
Combretum collinum Fresen.	Kalahari bushwillow	The stem bark powder mixture coupled with porridge or addition in tea is used to counter rectal collapse. Roots and leaves decoctions are consumed for the management of malaria. Root maceration or decoction is ingested to treat gonorrhea, female sterility, and pyomyositis. The juice extract from the roots is applied externally to toothache, snakebite wounds, and syphilitic sores (Adamu *et al.*, 2005; Katerere *et al*., 2003, 2012; Marquardt *et al.*, 2020; Masoko *et al.*, 2007).	Ethanol and crude extracts of fresh shoot bark have shown striking and dose-dependent larvicidal properties on the instar larvae of the yellow fever mosquito. Different leaf extracts have exhibited weak *in vitro* antifungal and anthelmintic activities. Aqueous root and stem bark extracts have shown antimicrobial activity against *Proteus mirabilis* (Adamu *et al.*, 2005; Katerere *et al.*, 2003). Extracts exhibited antimicrobial activities against *Escherichia coli*, *S. aureus*, *Candida albicans*, *Mycobacterium fortuitum*, and *Proteus vulgaris* (Katerere *et al.*, 2012). Isolated compounds had MIC values of <200 µg/ml against *Pseudomonas aeruginosa*, *S. aureus*, *E. faecalis*, and *E. coli*.	Triterpenoids in the leaves (Rogers and Coombes, 1999). Stilbenoids combretastatins A and B and phenanthrenes (Katerere *et al.*, 2003). 9,10-Dihydro-3,6,7-trimethoxy-2,5-phenanthrenediol (Katerere *et al.*, 2012). Two bibenzyls: 5′-hydroxy-3,4,4′,5-tetramethoxybibenzyl; 1a,3′-dihydroxy-3,4,4′,5-tetramethoxybibenzyl (Katerere *et al.*, 2012).
Combretum erythrophyllum (Burch) Sond.	River bushwillow	The roots are used to treat venereal disease. Coughs and stomach pains have been cured using the leaf extract. Poisonous seeds are used for dogs' intestinal worms purgative. Management of cough and unproductiveness, as well as an aphrodisiac, has been achieved using elixir from roots and bark (Aderogba *et al.*, 2012; Arnold and Gulimian, 1984; Martini and Eloff, 1998; Mtunzi *et al.*, 2017a, 2017b; Schwikkard *et al.*, 2000; Van Wyk and Van Wyk, 1997).	Rhamnocitrin and rhamnazin demonstrated robust antioxidant activity with prospective anti-inflammatory activity. Microdilution assay of dried leaf acetone extract exhibited an LC_{50} of 1.50 mg/ml on *S. aureus, P. aeruginosa*, and *E. faecalis*, while 0.8 mg/ml was observed for *E. coli* (Eloff, 1998). The toxicity level of *C. erythrophyllum* (Burch.) crude extract and portions investigated in Vero monkey kidney cells stretched from 34 to 223 mg/ml (Mtunzi *et al.*, 2017b). Extracts of chloroform, hexane, butanol, acetone, and carbon tetrachloride solvents have revealed antibacterial activities against *E. coli, P. aeruginosa*, *E. faecalis*, *S. aureus* at different concentrations (Eloff, 1998; Martini and Eloff, 1998).	Four flavonols: kaempferol, rhamnazin, 5,3′-dimethylether, quercetin, and rhamnocitrin, Three flavones: genkwanin, apigenin, and 5-hydroxy-7,4′-dimethoxyflavone (Martini *et al.*, 2004a, 2004b). Triterpene (Mtunzi *et al.*, 2017c). Combretastatin A-1 and (-)-combretastatin (Schwikkard *et al.*, 2000). 3-Oxo-cycloart-1,11,24-trien-23,21-olide (Rogers, 1998).

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Combretum species	Common name	Ethnobotanical use	Biological activity	Bioactive compounds isolated
Combretum fragrans F. Hoffm.	Four-leaved bushwillow	Root decoctions are ingested to manage syphilis, cough, and leprosy. Cleansing of chronic wounds was achieved using leaf decoctions. Methanolic extracts of the barks and stem have been used to treat blackleg in animals (Dawe *et al.*, 2016; Maima *et al.*, 2008; Useh *et al.*, 2004).	Root extracts exhibited antibacterial activity against *Shigella boydii*, *Klebsiella pneumonia,* and *S. aureus* (Chhabra *et al.*, 1984). Stem bark fractions have shown *C. chauvoei* neuraminidase inhibition, significant for handling blackleg in sheep, cattle, and other ruminants (Maima *et al.*, 2008). Methanol extracts from dried leaves or roots have exhibited cytotoxicity.	Roots contain flavonoids, anthracene glycosides, tannins, coumarin, starch, and triterpenoids (Chhabra *et al.*, 1984).
Combretum griffithii Van Heurck & Müll. Arg.	Lianas woody	Stem-Water decoction has been utilized locally as a management against hepatitis Bark, root, stem, and leave decoction extracts have been used for malarial cough treatment (Moosophon *et al.*, 2011).	Methanol extract of the stem has displayed cytotoxicity against oral human epidermal carcinoma cell lines (LC_{50} = 2.6 µg/ml) and antimycobacterial assay with MIC 3.13 µg/ml (Moosophon *et al.*, 2011).	Arylpropyl quinone; 1-(2-hydroxy-4-methoxyphenyl)-3-(4-hydroxy-3-methoxyphenyl) propane; 1-(4,5-dihydroxy-2-methoxyphenyl)-3-(3,4-dimethoxyphenyl)propane; 1-(3-hydroxy-2,4-dimethoxyphenyl)-3-(4-hydroxy-3-methoxyphenyl) propane; 1-[2-(5-methoxy-1,4-benzoquinone)]-3-(4-hydroxy-3-methoxyphenyl)propane, and 1-(4-hydroxy-2,5-dimethoxyphenyl)-3-(4-hydroxy-3-methoxyphenyl)propane (Moosophon *et al.*, 2011).
Combretum imberbe Wawra	Leadwood	Leave and root decoction extracts are used to manage diarrhea and cough. Ashes of wood are used as toothpaste (Eloff *et al.*, 2008). Root infusion was used to treat schistosomiasis; root maceration was used to treat stomach aches; infertility in women for gynecological complaints (McGaw *et al.*, 2001; Roy *et al.*, 2014a).	Five pentacyclic triterpenoids have displayed activities against *E. coli* and *S. aureus* (Angeh *et al.*, 2007a). Pentacyclic triterpenes, glycosides based on imberbic acid and glycosidic derivatives of hydroxyimberbic acid exhibited bactericidal activities against *S. aureus* and *M. fortuitum* (Katerere *et al.*, 2003; Rogers, 1988). $MeCl_2$ extract of the leaf exhibited antibacterial action against *S. aureus* (MIC = 39 µg/ml) by microplate serial dilution method (Angeh *et al.*, 2007a). MeOH, hexane, $MeCl_2$, and acetone extracts of the leaf have demonstrated antifungal activity against *A. fumigates*, *C. albicans*, *A. fumigates*, *M. canis*, and *S. schenckii* by microdilution assay (Masoko *et al.*, 2007). Acetone extract of the dried leaf has been used for *in vitro* nematocidal activity via egg hatching and larval growth of *Haemonchus contortus-Lethal* (Ademola and Eloff, 2010).	1,3,24-Trihydroxyl-12-oleanen-29-oic acid, 1,3-dihydroxy-12-oleanen-29-oic1-hydroxy-12-olean-30-oic acid, 3,30-dihydroxyl-12-oleanen-22-one, 1,23-dihydroxy-12-oleanen-29-oicacid-3-0-2,4-di-acetyl-1-rhamnopyranoside (Angeh *et al.*, 2007a). 23-Hydroxyimberbic acid 3-*O*-α-l]-rhamnopyranoside 1-acetate and 23-hydroxyimberbic acid 23-*O*-α-l-rhamnopyranoside (Rogers, 1988).
Combretum kraussii Hochst.	Forest bushwillow	Aqueous bark, root, and leave extracts are used for fever, sawdust irritants, antiseptic, antidiuretic, and inflammation. Also, they are used for body pain by bathing in the root powder decoction (Masoko *et al.*, 2007; McGaw *et al.*, 2001).	Microdilution assay of dried leaf hexane, acetone, MeOH, and $MeCl_2$ extracts have exhibited antifungal activities on *A. fumigates* with MIC values of 2.5, 1.25, 0.64, 0.16, and 2.5 mg/ml, respectively (Masoko *et al.*, 2007; McGaw *et al.*, 2001). Acetone, water (H_2O), or AcOEt extracts of the leaf exhibited *in vitro* cyclooxygenase-1 (COX-1) via radioactivity bioassay, while water, acetone, and AcOEt extracts exhibited *in vitro* anthelmintic activity against morms of *C. elegans* var. Bristol (McGaw *et al.*, 2001).	3,3′-di-O-methylellagic acid; 3,3′,4′-tri-O-methylflavellagic acid; 3,4,3′-tri-O-methylflavellagic acid-4′-β-D-glucoside (Brookes *et al.*, 1999). Combretastin A (Rogers and Verotta, 1996).

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Combretum species	Common name	Ethnobotanical use	Biological activity	Bioactive compounds isolated
Combretum leprosum Mart.	Semideciduous tree	Aerial parts such as stems, leaves, flowers, and roots decoctions, and alcoholic extracts have been utilized as hemostatics and sedative agents for wound treatment during uterine bleeding. Aqueous extracts of diverse parts have been used as traditional remedies for treating numerous inflammatory infections (Facundo *et al.*, 2005; Moraes *et al.*, 2016; Nunes *et al.*, 2009; Teles *et al.*, 2015).	Ethanolic extract from flower parts induced antinociception in different prototypes of chemical and thermal pain in mice (Pietrovski *et al.*, 2006). Bark extract on isolated arterial rings from different animals caused relaxations (Filho *et al.*, 2015). Possible neuroprotective potentials of the ethanolic extract were investigated in a murine prototype of Parkinson's disease (Moraes *et al.*, 2016).	Pentacyclic triterpene 3β, 6β, 16β-trihydroxylup-20(29)-ene, (Longhi-Balbinot *et al.*, 2009, 2011; Teles *et al.*, 2015). Cycloartanes, triterpenes (arjunolic and mollic acid, and 3β, 6β, 16β-trihydroxilup-20(29)-ene), and flavonoids (3-O-methylquercetin, and quercetin) (Facundo *et al.*, 1993).
Combretum micranthum G. Don	Bushy shrub or creeper	Leaf infusions are ingested against cold, colic, vomiting, fever, and gastrointestinal complications. Roots decoctions as anthelminthic and for washing and treatment of wounds. Aqueous, ethanol, chloroform, and methanol extracts have been used for the treatment of microbial attacks. Aqueous extracts of various plant parts have been used to treat malaria and bronchitis (Chika and Bello, 2010; De Morais Lima *et al.*, 2012; Marquardt *et al.*, 2020).	Aqueous and acetone extracts of leaves possess bactericidal potentials against *K. ozaenae*, *S. dysenteriae*, and *S. Paratyphi B* (Karou *et al.*, 2005). Different extracts of *C. micranthum*: ethanol, chloroform, methanol, or water exhibited notable antibacterial activity against *Salmonella species*, *P. aeruginosa*, *M. luteus*, *Streptococcus species*, *S. aureus*, *B. subtilis*, *Klebsiella species*, *Sarcina lutea*, and *P. vulgaris* (De Morais Lima *et al.*, 2012). Hypoglycemic activity has been observed for the leaves water extracts by stimulation of diabetes mellitus type 1 and 2 by alloxan in rats at doses: 100, 200, or 400 mg/kg (p.o.) (Chika and Bello, 2010).	Polyphenols exhibiting antioxidative properties (Karou *et al.*, 2005). 4-Hydroxyproline betaine (Ogan, 1972). 3′,4′,5,7-Tetrahydroxyflavan; homoorientin; 2″-O-galloylisovotexin; 3′,4′,5′,5,7-pentahydroxyflavan; orientin; 2″-O-galloylvotexin; myricetin-3-O-glucoside; 2″-O-galloylhomoorientin; Isovitexin; Kinkeloid A1–D2 (Welch, 2010). (-)-Epicatechin; (-)-epigallocatechin; vitexin (Angeh *et al.*, 2007a).
Combretum mkhuzense J.D. Carr & Retief	Maputaland bushwillow	Roots decoction is utilized as an aphrodisiac for the treatment of venereal syndrome and to purge patients of duodenal worms and microbial treatment (Gaidamashvili and Van Staden, 2002; McGaw *et al.*, 2001).	Activity against *B. subtilis* and *S. aureus* was displayed by the leaf extracts (Gaidamashvili and Van Staden, 2002). Isolated lectin-like proteins for COX exhibited *in vitro* COX-1 activity with 82% inhibition (Gaidamashvili and Van Staden, 2006). Leaf extracts were found to be active against *E. faecalis* (Eloff, 1998, 1999; Pegel and Rogers, 1985).	Lectins from leaf extracts (Gaidamashvili and Van Staden, 2002).
Combretum molle R. Br. ex G. Don.	Velvet bushwillow	The powdered root part is used as a wound dresser. Elixirs of the roots are used for leprosy, hookworm, fever, snakebite, general body swelling, stomach pains, and abortion (Fyhrquist *et al.*, 2006; Masoko and Eloff, 2007; Ntshanka *et al.*, 2020; Suleiman *et al.*, 2013).	Acetone portions of stem bark inhibited the development of *Mycobacterium ruberculosis* typus humanus (Asres *et al.*, 2001). Inhibits HIV-1 reverse transcriptase (Bessong *et al.*, 2005). Methanolic-aqueous extract of the stem bark has exhibited anthelmintic potentials in lambs infested with *H. contortus* via faecal egg count reduction assay (Simon *et al.*, 2012; Suleiman *et al.*, 2013). Acetone extract of the leaf part demonstrated 99.64% DPPH inhibition, while the antimicrobial activities of acetone, ethanol, and methanol extracts by broth dilution demonstrated activity against *P. aeruginosa* (39.06 mg/µl) and *E. coli* (78.13 mg/µl) strains, respectively (Ntshanka *et al.*, 2020).	Antifungal mollic acid: 3-β-D-glucoside (Pegel and Rogers, 1985) ; Combretene A and B (1–2); Polyhydroxyoleanane-type triterpenoids (Bahar *et al.*, 2005; Kemvoufo *et al.*, 2008). Punicalagin, hydrolyzable tannin, provides antimycobacterial properties (Asres *et al.*, 2001). Gallotannin (Bessong *et al.*, 2005). Alkaloids; flavonoids; cardiac glycosides; saponins; triterpenes (Simon *et al.*, 2008). Mollic acid and Arjunolic acid (Nyenje and Ndip, 2012).

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Combretum species	Common name	Ethnobotanical use	Biological activity	Bioactive compounds isolated
Combretum nigricans Lepr.	Fairly tall tree in the tiger bush	Aqueous leave extracts are used to treat stomach problems and as an expectorant. Also, used for the management of innumerable infections such as conjunctivitis, cataract, rheumatism, and icterus (Fyhrquist *et al.*, 2006; Simon *et al.*, 2003).	Methanolic fraction of the fresh leaves inhibited the development of human tumor cell lines: bladder (J82), colon (HCT-15), non-small-cell lung (A549), and glioblastoma (U-373), cancer models (Jossang *et al.*, 1996; Simon *et al.*, 2003). Ethanol/H_2O (1:1) extract of dehydrated root antifungal activities against *C. albicans*, *E. floccosum*, *T. mentagrophytes, M. gypseum*, *T. rubrum* via Microdilution assay (Baba-Moussa *et al*., 1999). Acetone leaves extracts showed antimicrobial activity with MIC of 0.8 mg/ml against *E. coli* and *E. faecalis* (Eloff, 1999).	Combregenin; arjungenin; arjunglucoside; combreglucoside mollic acid (Jossang *et al.*, 1996). 11α-Acetoxy-20,24-epoxy-25-hydroxy-dammar-3-one; Arcapitin A; 20,24-epoxy-11α,25-dihydroxy-dammar-3-one; 20,24-epoxy-12β,25-dihydroxy-dammar-3-one (Simon *et al.*, 2003).
Combretum padoides Engl. & Diels	Thicket bushwillow	Aqueous leaves and root extracts are utilized to treat conjunctivitis, snakebites, gastrointestinal complications, bloody diarrhea, and wounds, to eliminate hookworms, and as antimalarial (Ahmed *et al.*, 2014; Fyhrquist *et al.*, 2006; Gathirwa *et al.*, 2011; McGaw *et al.*, 2001).	Microdilution assay of dried leaves of acetone, hexane, $MeCl_2$, or MeOH extracts have exhibited antifungal activities against *A. fumigates*, *S. schenckii*, *M. canis*, *C. neoformans*, and *C. albicans* with MIC stretching from 0.02 to 2.5 mg/ml (Masoko *et al.*, 2007). Methanolic elixirs of dried root, leaves, and stem have displayed cytotoxicity activities against HeLa cervical, T24 bladder, and MCF7 breast cancer with an IC_{50} of 25 µg/ml (Fyhrquist *et al.*, 2006; Nopsiri *et al.*, 2014). Aqueous, acetone, and AcOEt extracts of the leaf have shown *in vitro* anthelmintic activity against worms of *C. elegans* var. Bristol, while aqueous extract exhibited *in vitro* antischistosomal against worms of *S. haematobium* (McGaw *et al.*, 2001)	1α,23-β-Dihydroxy-12-oleanen-29-oic acid; 23-β-*0*-α-4-acetylrhamnopyranoside; Ethylcholesta-7,22,25-trien-0-β-*D*-glucopyranoside; 1,22-dihydroxy-12-oleanen-30-oic acid; 24-ethylcholestα-7,22,25-triene-3-O-β-D-glucopyranoside (Angeh *et al.*, 2007b). Ellagitannin; ellagic acid arabinoside; corilagin; punicalagin; methyl ellagic acid xyloside (Fyhrquist *et al.*, 2020).
Combretum psidioides Welw.	Peeling bushwillow	Mixtures are used for coughs, chest problems, and pain treatment in the spinal cord, and root infusion is applicable. Aqueous leaves and root extract have been used for treating diarrhea, back pain, rheumatic pain, muscle pain, malaria, and derma. Hot water elixirs of roots and leaf extracts; or powdered fresh or dried leaves mixed with maize porridge (Ugali) have been used to manage diarrhea and edema (Fyhrquist *et al.*, 2006, 2020; Gessler *et al.*, 1994).	*In vitro* cytotoxicity potentials against T24 bladder, MCF7 breast, and HeLa cervical cancer (LC_{50} = 25 µg/ml) have been observed for methanolic extracts of dried stem bark, fruit, and root (Fyhrquist *et al.*, 2006; Nopsiri *et al.*, 2014). Aqueous, EtOH (95%), EtOAc, and Pet ether extracts of root bark have displayed *in vitro* antimalarial activity against *P. falciparum* by microdilution assay (IC_{50} for drugs: 6.5–39.0 µg/ml (Gessler *et al.*, 1994) Crude methanol extract; its $CHCl_3$ and butanol portions have exhibited development inhibitory activity against *Mycobacterium smegmatis* with MIC values stretching from 625 to 2,500 µg/ml (Fyhrquist *et al.*, 2020).	2,6,7-Trihydroxy-3,4-dimethoxyphenanthrene; 7-hydroxy-2,3,4,6-tetramethoxyphenanthrene; 7-hydroxy-2,3,4,6-tetramethoxy-9,10-dihydrophenanthrene; 2,7-dihydroxy-3,4,6-trimethoxyphenanthrene; 7-hydroxy-2,4,6-trimethoxy-9,10-dihydrophenanthrene; 7-hydroxy-2,4,6-trimethoxyphenanthrene; 2,6,7-trihydroxy-3,4-dimethoxy-9,10-dihydrophenanthrene (Kovács *et al.*, 2008). 4′-Hydroxy-3,4,5-trimethoxybibenzyl and 4,4′-dihydroxy-3,5-dimethoxybibenzyl (Letcher and Nhamo, 1972). Combretastatin B-2 and dihydrostilbene derivatives; punicalagin; sanguiin H-4; corilagin (Fyhrquist *et al.*, 2020).

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Combretum species	Common name	Ethnobotanical use	Biological activity	Bioactive compounds isolated
Combretum rotundifolium Rich.	Shrub or climbing plant Monkey brush vine	Crushed stem decoction is applied externally as a febrifuge. The sap is rubbed onto the forehead to lessen the headache. The flowers are chewed to reinforce gums that are bleeding and weak (Dawe *et al.*, 2013; Rogers, 1995; Roy *et al.*, 2014a).	The plant is reaped from the wild for indigenous medicinal use	(16r)-16-*O*-α-L-arabinosyl-3*β*--hydroxymansumbin-13-en-28-oic acid and (16r)-16-*O*-α-L-arabinofuranosyl-3*β*-hydroxydammarα-20,24-dièn-29-oic acid (Rogers, 1995; Roy *et al.*, 2014a).
Combretum quadrangulare Kurz.	Shrub or small tree	Stems, leaves, seeds, and bark of the specie have been utilized as antidysenteric, antiascariasis, antipyretic, antibacterial, anthelmintic, antihepatitis, and antiparasitic agents. The seeds are orally administrated alongside ripe bananas as an anthelmintic for oxyuriasis and ascariasis (Adnyana *et al.*, 2000b; Banskota *et al.*, 2000; Roy *et al.*, 2014a).	Seeds methanolic extract of *C. quadrangulare* has exhibited effective hepatoprotective activity against TNF-α) or D-galactosamine-induced cell death in main cultured mouse hepatocytes (Adnyana *et al.*, 2000a, 2001a). Dried leaf dichloromethane extract evaluated for its antioxidant potentials gave an ABTS and DPPH radical scavenging capacity with LC_{50}– dose of 76.62 ± 0.0040 and 5.16 ± 0.0169 µg/ml, respectively (Nopsiri *et al.*, 2014; Roy *et al.*, 2014b). Ethanolic (95%) and H_2O extracts of dried leaf exhibited an *in vitro* HIV-1 integrase inhibition via cell culture with an LC_{50} of 2.5 µg/ml for ethanolic (95%) extract and 2.9 µg/ml for H_2O extract (Roy *et al.*, 2014b; Tewtrakul *et al.*, 2003). Ethanolic extract of the dried leaf via Agar disc diffusion method showed MIC: <0.125 mg/ml and zone of inhibition of 10.0 ± 0.5 mm against *E. coli*, while activity against *B. subtilis* showed MIC: <0.004 mg/ml and zone of inhibition: 18.7 ± 0.8 mm (Masengu *et al.*, 2014).	Three triterpenes: 6β-hydroxyhovenic acid, lupane type, 2α,6β-dihydroxybetulinic acid, and an oleanane type, 6β-hydroxyarjunic acid (Adnyana *et al.*, 2001a). Nine new: combretanones A-G (1-7), cycloartane triterpenes, combretic acid A (8), and combretic acid B (9) (Toume *et al.*, 2011). 1α,3β-dihydroxy-cycloart-24-ene-30-carboxylic acid methyl ester; 4β,14α-dimethyl-5α-ergostα-9β,19-cyclo-24(31)-en-3β-hydroxy-4α-carboxylic acid; 2α,3β,23-trihydroxyurs-12,19-dien-28-oic acid β-d-glucopyranosyl; 3′,5-dihydroxy-3,4′,5,7-tetramethoxyflavone; 1-O-galloyl-6-O-(4-hydroxy-3,5-dimethoxy) benzoyl-β-D-glucose; 5,7,3′,5′-tetrahydroxy-3,4′-dimethoxyflavone; 28-O-β-d-glucopyranosyl-6β,23-dihydroxytormentic acid (Adnyana *et al.*, 2000a, 2000b, 2001b; Banskota *et al.*, 2000; Ganzera *et al.*, 1998; Toume *et al.*, 2011; Roy *et al.*, 2014a, 2014b).
Combretum vendae A.E. van Wyk	Venda bushwillow	Aqueous extract of the roots and leaf has been utilized to cure bacterial-related contaminations and oxidative-related diseases such as pneumonia, syphilis, chest, diarrhea, coughs, and colds (Ahmed, 2012; Dawe *et al.*, 2013; Komape *et al.*, 2014).	Fractions of the leave parts had MIC values of 160 µg/ml (*S. aureus*), 320 µg/ml (*E. faecalis*), >320 µg/ml (*P. aeruginosa*), and 320 µg/ml (*E. coli*), also possess antifungal activities (Ahmed *et al.*, 2009; Suleiman *et al.*, 2010) Ethyl acetate fractions have displayed antiradical activity with the EC_{50} lower or comparable to the control (Ahmed, 2012). Hexane, methanol, dichloromethane, chloroform, and acetone of the leaves showed antibacterial potentials against *E. faecalis*, *E. coli*, *S. aureus*, and *P. aeruginosa* by serial microplate dilution method (Komape *et al.*, 2014). Methanolic extract of the leaf part showed DPPH radical scavenging potential (Lawal *et al.*, 2016).	Apigenin (Eloff *et al.*, 2008; Komape *et al.*, 2014). Acacetin (Komape *et al.*, 2014). Corosolic acid, arjunolic acid, combretastatin B5-O-2′-beta glucopyranoside, ursolic acid; maslinic acid, and combretastatin B1-O-2′-beta glucopyranoside (Ahmed, 2012; Dawe *et al.*, 2013; Roy *et al.*, 2014a).

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Combretum species	Common name	Ethnobotanical use	Biological activity	Bioactive compounds isolated
Combretum woodii Dümmer	Large-leaved forest bushwillow	Leaves and barks extracts are used to manage chest complaints/pains, and microbial infections (Eloff *et al.*, 2005; Masoko and Eloff, 2007; McGaw *et al.*, 2001).	Combretastatin B5 showed a MIC = 16 µg/ml against *S. aureus*, while 125 µg/ml was observed against *E. faecalis* and *P. aeruginosa* (Eloff *et al.*, 2005). Aqueous, acetone, and AcOEt leaf extracts using radioactivity bioassay have exhibited *in vitro* COX-1 inhibition; and *in vitro* anthelmintic against larvae of *C. elegans* var. Bristol at concentrations of 0.5 and 1 mg/ml (McGaw *et al.*, 2001). Ethyl acetate fraction demonstrated an average MIC of 50 µg/ml against *E. coli*, *P. aeruginosa, E. faecalis, S. aureus*, acetone, and methylene dichloride fractions with MIC = 140 µg/ml. Fractions of acetone and methylene dichloride gave a total activity of 1,279 and 1,309 ml/g (Eloff *et al.*, 2005). Acetone, DCM, and methanol elixirs demonstrated antioxidant activity after squirting chromatograms with DPPH (Masoko and Eloff, 2007).	Combretastatin B5; A stilbene; bibenzyl (Eloff *et al.*, 2005). Combretastatin B5 (Karatoprak *et al.*, 2020).
Combretum yunnanense Exell	Forests, sparse forests, woods		Sequestered compounds from the ethanolic leaves extract and stems have displayed cytotoxicity *in vitro* against five human cancer cell lines: SMMC-7721, MCF-7, A-549, SW480, and HL-60 (Wu *et al.*, 2011).	Combregenin, arjungenin, arjunglucoside I, combreglucoside, betulinic acid, arjunic acid, arjunetin, asiatic acid, ursolic acid, and maslinic acid (Wang *et al.*, 2011). 2,4,4′-Trihydroxychalcone, 1-(2-methoxy-4-hydroxyphenyl)-3-(3-hydroxy-4-methoxyphenyl)-propane, eriodictyol, and combrequinone A–C (Wu *et al.*, 2011). Combretol A–E; *β*-sitosterol; Scopoletin (Wang *et al.*, 2011). 4-(*α*-Rhamnopyranosyl)ellagic acid; ellagic acid; 4-(4″-*O*-acetyl-*α*-rhamnopyranosyl)ellagic acid (Asami *et al.*, 2003).
Combretum zeyheri Sond.	Large-fruit bushwillow or Raasblaar	Inhalation of the burnt leaves smokes for the cure of coughs. Colic is alleviated with the unpleasant-tasting water extracts of dried pulverized and root infusion leaves. Also, for the treatment of bloody diarrhea (Ahmed, 2012; Roy *et al.*, 2014a).	Acetone leaf extracts possess some antibacterial potential (Eloff, 1999). *Bacillus subtilis* and *E. coli* by agar disc diffusion method exhibited MIC = less than 0.125 mg/ml and MIC = less than 0.004 mg/ml, respectively, with inhibition zone (18.5 ± 0.5 mm). *Candida albicans* (MIC: 0.03 mg/ml) (Masengu *et al.*, 2014). Methanolic extracts of root and fruits exhibited *in vitro* cytotoxicity on MCF7 breast cancer cells with LC_{50} value of 25.00 µg/ml (Nopsiri *et al.*, 2014).	Arcapitin A (Facundo *et al.*, 2008). Oleanolic acid; terminolic acid; 6β-hydroxymaslinic acid; 2α,3β-dihydroxyurs-12-en-28-oic acid; methylsumaresinolate (Ahmed, 2012; Runyoro *et al.*, 2013). Maslinic acid (Runyoro *et al.*, 2013).

EC_{50}/LC_{50} = half maximal effective concentration; MIC = minimal inhibitory concentration; mg/ml = milligram per milliliter; µg/ml = microgram per milliliter; ml/g = milliliter per gram.

C. molle against stomach disorders; *C. molle, C. imberbe,* and *C. erythrophyllum* against coughs (Eloff *et al.*, 2008).

The medicinal benefits of *Combretum* species lie in some vital chemical constituents responsible for certain physiological exploit on the human body (Edeoga *et al.*, 2005; Filho *et al.*, 2015; Masoko *et al.*, 2007; Masoko and Eloff, 2007; Nagata *et al.*, 2011; Uzor and Osadebe, 2016) and are significant in pharmacological research and drug development (Ademola and Eloff, 2010; Moraes *et al.*, 2016; Roy *et al*., 2014a, 2014b). *Combretum* species possess extractable organic substances in quantities sufficient to exhibit antimicrobial activities (Adamu *et al.*, 2005; Katerere *et al.*, 2003; Masika and Afolayan, 2002; Olukoya *et al.*, 1993). Chemicals constituents from *Combretum* species hold complex arrangements that are not obtainable in synthetic compound collections; hundreds of chemical constituents have been consequential for use as antibacterial agents and other drugs (Aderogba *et al.*, 2012; Facundo *et al.*, 1993; Katerere *et al.*, 2012; Kgatle, 2007; Longhi-Balbinot *et al.*, 2009, 2011; Sabo and Knezevic, 2019; Welch, 2010). The species of *Combretum* has featured conspicuously as an agent for handling infectious diseases as exemplified in Table 1.

Evidence for medical efficacy of Combretum species

Phytochemical investigations to determine the medical efficacy of *Combretum*, the most widespread genus of Combretaceae, has paved the way several constituents comprising flavonoids, triterpenoids, phenanthrenes and their derivatives, diarylpropanes, and stilbenoids and their derivatives. Isolates or extracts from this class of species have shown several bioactivities, including antibacterial, antiradical, antifungal, antidiabetic, antihyperglycemic, cytotoxicity, and inhibitory activities, against different human tumor cell lines, anti-inflammatory, antimalarial, anti-snake venom, and anti-HIV/AIDS properties. Also, they have been used for the management of diverse infirmities and diseases (Aderogba *et al.*, 2012; Ares *et al.*, 2006; Belkaid and Hand, 2014; Chika and Bello, 2010; Dawe *et al.*, 2013; De Morais Lima *et al.*, 2012; Kemvoufo *et al.*, 2008; Khumalo *et al.*, 2018; Masoko *et al.*, 2007; Motsumi *et al.*, 2020; Nagata *et al.*, 2011; Uzor and Osadebe, 2016). Antidiabetic activity through adenosine monophosphate-activated protein kinase activation by quercetin from flower extracts of *C. lanceolatum* has been reported (Dechandt *et al.*, 2013). Anti-candidiasis agents from African Tanzanian plant: *C. zeyheri* (Runyoro *et al.*, 2013), while lignin derivative from *C. alfredii* (Bai *et al.*, 2016). *Combretum* species have also shown great potential as a source of various secondary metabolites. Metabolites and their related endophytic fungus *Nigrospora oryzae* as proof of a metabolic conglomerate from *C. dolichopetalum* have been reported by Uzor *et al.* (2015).

Studies on the antioxidant, antibacterial, cytotoxicity, and antifungal potentials of solvent-to-solvent fractionations of *C. erythrophyllum* (Burch.) leave elixirs revealed that *Combretum* species are nontoxic for usage in traditional medicine for the management of infectious and stress-related diseases (Mtunzi *et al.*, 2017b). Methanolic extract of the *C. adenogonium* Steud. ex A. Rich stem barks inhibited *C. chauvoei* (Jakari strain) neuraminidase activity as reported by Useh *et al.* (2004) at 100–1,000 μg/ml with an estimated LC_{50} value of 150 μg/ml. Extracts from the stem bark, root, and leaf have the potential as antibacterial, antifungal, and antiproliferative agents (Fyhrquist *et al.*, 2006; Maregesi *et al.*, 2007). Ethanolic stem bark, root, and leaf elixirs have displayed antibacterial by microdilution methods, an anti-HIV-1 protease with LC_{50} value of 24.7 and 26.5 μg/ml for root and stem bark extracts, respectively, and cytotoxic activities using brine shrimp's lethality assay (Mushi *et al.*, 2012).

Acetone elixir of *Combretum mole* stem bark had inhibited the evolution of *Mycobacterium Tuberculosis* typus humanus (ATCC 27294) (Asres *et al.*, 2001), inhibits HIV-1 reverse transcriptase (Bessong *et al.*, 2005). Aqueous-methanol stem bark elixir of *C. mole* has exhibited anthelmintic activity in infected lambs with *H. contortus* via faecal egg count reduction test (Simon *et al.*, 2012; Suleiman *et al.*, 2013). Interestingly, powdered and decoctions of *C. mole* root part have been used as a wound dresser for treatments of leprosy, fever, snake bite, stomach pains, all-purpose body swelling, hookworm, and abortion, While the activities of this *C. mole* associated with bioactive compounds such as hydrolysable tannin and punicalagin demonstrated antimycobacterial properties (Asres *et al.*, 2001). Compounds such as maslinic acid, ursolic acid; combretastatin B5-O-2′-beta glucopyranoside, corosolic acid, arjunolic acid, combretastatin B1-O-2′-beta glucopyranoside (Ahmed, 2012) isolated from *C. vendee* A.E. van Wyk have exhibited antimicrobial and antifungal activities (Ahmed *et al.*, 2009; Suleiman *et al.*, 2010); antiradical activity with the EC_{50} lesser or analogous to the control (Ahmed, 2012).

CONCLUSION

The reports detailed in this review advocate using medicinal plants as alternative medicine. *Combretaceae* species has displayed a broad spectrum of ethnopharmacological potentials for treating infectious diseases, exhibits significant antimicrobial and antifungal potentials against varieties of bacterial and fungal species, respectively, and also exhibit good antioxidant, anti-inflammatory, antimalarial, antituberculosis, antidiarrhoea, cytotoxicity, anthelmintic, antischistosomal, COX-1 inhibition, and HIV-1 integrase inhibition. Phytochemical constituents of the species are great prospective agents for averting and treating many related oxidative stress diseases. Even though the oils from some of these species have not been harnessed as a fragrance in the perfumery, food, and beverage industry; the oils and active compounds may also possess great potential for protecting food and cosmetics from microbial spoilage. Hence, medicinal plants can be seen as an alternative to medicine if properly used as prescribed or as a precursor for synthesizing chemotherapeutic agents for disease control. Concerning the above investigation, it is evident that *Combretaceae* species contain bioactive compounds such as triterpenoids, glycosylated triterpenes, and phytochemical constituents of biological importance. Given these outstanding values, few pharmacological and phytochemical analyses have been conducted. Hence, it will greatly benefit the health sector and medicinal chemistry if further research is encouraged and carried out toward identifying bioactive compounds and corroborating their medicinal and pharmacological properties. Areas of research in the economy, domestication, and proliferation, as well as quality control and procedures for sustainable utilization of these plant species as future potential antibiotic and chemotherapeutic agents, should be prioritized. This should be a priority for researchers and stakeholders as these plants can increase the well-being of the populace who finds solace in them.

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