Journal of Ethnopharmacology 305 (2023) 116004

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jethpharm

The African cherry: A review of the botany, traditional uses, phytochemistry, and biological activities of *Prunus africana* (Hook. *f.*) Kalkman

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A R T I C L E I N F O

Keywords:
Ethnopharmacology
Biological activities
African cherry
Prunus africana
Phytosterols
Phytochemistry
Clinical trials

A B S T R A C T

Ethnopharmacological relevance: Prunus africana (Hook.f.) Kalkman (Rosaceae), commonly known as "Pygeum" or "African cherry", occurs in mainland montane forests scattered across sub-Saharan Africa, Madagascar, and some surrounding islands. Traditionally, decoctions of the stem-bark are taken orally for the treatment of a wide variety of conditions, such as benign prostatic hyperplasia (BPH), stomach ache, chest pain, malaria, heart conditions, and gonorrhoea, as well as urinary and kidney diseases. The timber is used to make axe handles and for other household needs. The dense wood is also sawn for timber.

Aim: The fragmented information available on the ethnobotany, phytochemistry, and biological activities of the medicinally important *P. africana* was collated, organised, and analysed in this review, to highlight knowledge voids that can be addressed through future research.

Materials and methods: A bibliometric analysis of research output on *P. africana* was conducted on literature retrieved, using the Scopus® database. The trend in the publications over time was assessed and a network analysis of collaborations between countries and authors was carried out. Furthermore, a detailed review of the literature over the period 1971 to 2021, acquired through Scopus, ScienceDirect, SciFinder, Pubmed, Scirp, DOAJ and Google Scholar, was conducted. All relevant abstracts, full-text articles and various book chapters on the botanical and ethnopharmacological aspects of *P. africana*, written in English and German, were consulted.

Results: A total of 455 documents published from 1971 to 2021, were retrieved using the Scopus search. Analysis of the data showed that the majority of these documents were original research articles, followed by reviews and lastly a miscellaneous group comprising conference papers, book chapters, short surveys, editorials and letters. Data were analysed for annual output and areas of intense research focus, and countries with high research output, productive institutions and authors, and collaborative networks were identified. *Prunus africana* is reported to exhibit anti-inflammatory, analgesic, antimicrobial, anti-oxidant, antiviral, antimutagenic, anti-asthmatic, anti-androgenic, antiproliferative and apoptotic activities amongst others. Phytosterols and other secondary metabolites such as phenols, triterpenes, fatty acids, and linear alcohols have been the focus of phytochemical investigations. The biological activity has largely been ascribed to the phytosterols (mainly 3-β-sitosterol, 3-β-sitostenone, and 3-β-sitosterol-glucoside), which inhibit the production of prostaglandins in the prostate, thereby suppressing the inflammatory symptoms associated with BPH and chronic prostatitis.

Conclusions: Many of the ethnobotanical assertions for the biological activity of *P. africana* have been confirmed through *in vitro* and *in vivo* studies. However, a disparity exists between the biological activity of the whole extract and that of single compounds isolated from the extract, which were reported to be less effective. This finding suggests that a different approach to biological activity studies should be encouraged that takes all secondary metabolites present into consideration. A robust technique, such as multivariate biochemometric data analysis, which allows for a holistic intervention to study the biological activity of a species is suggested.

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https://doi.org/10.1016/j.jep.2022.116004
Received 23 August 2022; Received in revised form 28 November 2022; Accepted 29 November 2022
Available online 16 December 2022
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Furthermore, there is a need to develop rapid and efficient quality control methods for both raw materials and products to replace the time-consuming and laborious methods currently in use.

List of abbreviations:

AA	atraric acid
AR	androgen receptor
ATCC	American Type Culture Collection
ADA	Austrian Development Agency
b-FGF	basic fibroblast growth factor
BPH	benign prostatic hyperplasia
CC_{50}	half maximal cytotoxic concentration
CIFOR	Centre for International Forestry Research
CITES	Convention on International Trade in Endangered Species
DHT	dihydrotestosterone
DRC	Democratic Republic of the Congo
DPPH	2,2-diphenyl-1-picrylhydrazyl
EGF	epidermal growth factor
ESCOP	European Scientific Cooperative on Phytotherapy
FGF2	fibroblast growth factor 2
FID	flame ionization detector
FT-IR	Fourier transform infrared
GC–MSD	gas chromatography-mass selective detector
HIV	human immunodeficiency virus
HPLC	high performance liquid chromatography
HPTLC	high performance thin layer chromatography
HSV	herpes simplex virus; I/R, ischemia/reperfusion
ICRAF	International Centre for Research in Agroforestry
IgE	immunoglobulin E
IPSS	International Prostate Symptom Score
IUCN	International Union for Conservation of Nature
LC–MS	liquid chromatography coupled to mass spectrometry
LPS	lipopolysaccharide
LUTS	lower urinary tract symptoms
MIC	minimum inhibitory concentration
MMC	mutagen mitomycin C
MRSA	methicillin-resistant *Staphylococcus aureus*
NBBS	*N*-butylbenzenesulfonamide
OTC	Over-the-Counter; QC, quality control
RT-PCR	reverse transcriptase-polymerase chain reaction
TGFB1	transforming growth factor B1
TLC	thin layer chromatography
WHO	World Health Organization
ZI	zone of inhibition

1. Introduction

Traditional medicine practitioners continue to be the main source of medical care for a large proportion of the developing world population. In Africa, indigenous plants play an important role in the traditional treatment of diseases (Phillipson, 1994). According to the World Health Organization (WHO), over 21,000 plant species have medicinal uses throughout the world (Noor et al., 2013). Traditional medicines from diverse natural sources, including flora, fauna and fungi have been well documented (Bodeker et al., 2005; Alves and Rosa, 2007; Alves et al., 2013). International interest in researching, recognising, supporting, and promoting the use of traditional, complementary, and alternative medicine is continually expanding, and in many instances, trade is adversely affecting the sustainability of natural resources. There are numerous reasons for the renewed awareness of natural products as medicines. For example, microbial resistance to antibiotics is a global threat to health and development (World Health Organization, 2021), and has, since the beginning of the 21st century, sparked renewed interest in the consideration of plants and other natural sources as potential antimicrobial agents. Pharmaceutical companies with a commercial interest, healthcare practitioners, and patients all stand to benefit from the discovery of new drug compounds and lead molecules (Gowan, 2001).

Prunus africana (Hook.f.) Kalkman (formerly *Pygeum africanum* or *Laurocerasus africana* (Hook.f.) Browicz), commonly known as the African cherry, African plum, African prune, or bitter almond, belongs to the Rosaceae family, subfamily Amygdaloideae syn. Prunoideae, subgenus *Laurocerasus* (Kalkman, 1966; Gurib-Fakim, 2006). The word "*Prunus*" is derived from the plum-like shape which is characteristic of the genus of its fruit and "*africana*" refers to the fact that the tree is endemic to the montane forests of Africa (Graham, 1960). *Prunus africana* is scattered in Afromontane Forest "islands" across Africa (Angola, Burundi, Cameroon, South Africa, Ethiopia, Ghana, Kenya, Lesotho, Malawi, Mozambique, Rwanda, Tanzania, Uganda, Zambia, Democratic Republic Congo, Zimbabwe, and Madagascar), as well as some offshore islands. It has multiple uses, both medicinal and for household purposes (Cunningham and Mbenkum, 1993; Stewart, 2003). The tree is highly sought after, due to its plethora of traditional uses including the treatment of benign prostatic hyperplasia (BPH) (Keehn and Lowe, 2015; Komakech et al., 2017; Komakech and Kang, 2019; Nambooze et al., 2022). Extracts from the stem-bark and root-bark contain a range of secondary metabolites with reported anticancer, analgesic, anti-inflammatory, antimicrobial and antiviral activities. In traditional medicine systems, the species is relied on to treat malaria, fevers, mental illness, and in particular gastrointestinal disorders, ranging from abdominal pain to intestinal parasites in children (Stewart, 2003; Odongo et al., 2022). It is also used as an aphrodisiac (Vinceti et al., 2013).

In the 1970s, the commercial use of *P. africana* began with the marketing of a bark extract as an effective treatment for BPH and related conditions. These extracts were patented and have been successfully marketed in the Western world for many decades. *Prunus africana* herbal medicinal products are approved by numerous medicine regulatory authorities and are formulated into more than 40 trademarked capsules, tablets, and liquid extracts in France, Greece, Poland and the Czech Republic, with labelling approval to treat mainly lower urinary tract symptoms (LUTS) and micturition disorders associated with BHP (European Medicines Agency, 2015; Cunningham et al., 2016). Western pharmaceutical companies first recognised the medicinal value of *P. africana* almost 50 years ago, and current trade in this plant is worth millions of dollars (Simons et al., 1998; Nzilani, 1999). Cunningham et al. (1997) estimated the over the counter (OTC) value of the *P. africana* products trade as $220 million per annum. More recent valuations are needed. But what is known is that *P. africana* is Africa's most valuable medicinal export plant. Historically, Cameroon has been the major exporter of *P. africana* bark and commercial overexploitation of wild populations of *P. africana* has been rife for decades (Cunningham and Mbenkum, 1993; Cunningham et al., 2016). The shift from wild harvest to commercial cultivation is economically viable and *P. africana* plantation trials in Kenya date back to 1919 (Cunningham et al., 2002; Franzel et al., 2014). Local farmers have cultivated *P. africana* in

agroforestry systems in Cameroon since the mid-1970s (Cunningham et al., 2002) and more recently in Uganda as part of a carbon credits project (Orrego, 2005). Despite significant stocks of cultivated *P. africana* grown by smallholder farmers in north-western and south-western Cameroon, elite capture of the supply chain has been a major barrier to establishing sustainable and more equitable supply chains (Cunningham et al., 2016).

Due to commercial overexploitation and the medicinal importance of *P. africana*, research since the early 1990s has focussed on domestication and sustainability. Complementary studies on *P. africana* genetic diversity have also been conducted during this time as a means to domestication and conservation. Barker et al. (1994) pioneered studies of *P. africana* populations in East and southern Africa. More recently, Kadu et al. (2012, 2013) studied *P. africana* genetics across Africa, with Mbatudde et al. (2012) focusing on *P. africana* genetics in East Africa and Nzweundji et al. (2020) conducting related research in western Cameroon.

This review provides a bibliometric assessment of the available research on *P. africana* and provides insights on the global distribution of publications, research focus areas, as well as author and country collaboration networks. In addition, the review comprehensively assembles the fragmented information on botanical aspects, ethnopharmacology, phytochemistry and biological activities of *P. africana*. Biopharmaceutical characteristics and toxicity aspects related to the species, which are essential parameters in drug delivery, drug action and use, are also discussed. Quality control (QC) measures, which form an integral part of product development and production, are also addressed, and potentially useful methods for the QC of *P. africana* are evaluated.

2. Methods

To understand the global status of *P. africana* research, a bibliometric study of literature published on the species was undertaken. Publications were retrieved from the Scopus database (Elsevier, Netherlands) using the search string (TITLE-ABS-KEY ({*Prunus africana*}) OR TITLE-ABS-KEY ({*Pygeum africanum*})). The search identified 455 publications, which were subjected to descriptive bibliometric analysis and mapping. Quantitative descriptors such as publications per year, type of publication, most productive authors, institutions, and countries were obtained using the built-in 'data analysis' function. In VOSviewer (CWTS, Netherlands) the keywords and abstracts were analysed to generate network term maps, and the bibliographic data was used to assess collaborations between authors and countries.

The words "African cherry" and "*Prunus africana*" were also used as search terms ("all fields") to access other databases, including Web of Science, ScienceDirect, SciFinder, Pubmed, Scirp, DOAJ, and Google Scholar. No specific time frame was set to limit the search. All relevant abstracts, full-text articles and various books, written in English and German, were consulted that contained botanical and ethnopharmacological information on *P. africana*.

3. Bibliometric overview of *Prunus africana* research

The Scopus search retrieved 455 documents published from 1971 to 2021. Analysis of the data showed that the majority of these documents were original research articles (63.1%) followed by reviews (27.7%) and lastly a miscellaneous group (9.2%) comprising conference papers, book chapters, short surveys, editorials, and letters. The data were further analysed for annual output and to identify areas of intense research focus, countries of influence, productive institutions and authors, and collaborative networks. A breakdown of the annual publication output showed a low output over the period 1971–1994, with an average of only 2.1 publications per year (Fig. 1). However, an incremental growth was observed from 1995, as output increased from single to double digits, with a sudden peak of 32 publications in 2002. A closer analysis of the 2002 output revealed that the majority of publications were reviews (53%) that focussed on phytotherapy and treatment interventions for BPH. These reviews seemed to have stimulated research interest in *P. africana*, paving the way for researchers to explore the scientific basis for its use in the management of BHP. From 2003 to 2014, the publication output fluctuated with an average of 18.5 publications per year. A sharp decline was observed from 2015 to 2018, with a subsequent steady increase until 2020 and finally, a low output in 2021. The trend shows that research on *P. africana* has taken a slow pace over the past few years, which may be due to two factors. Firstly, bureaucratic

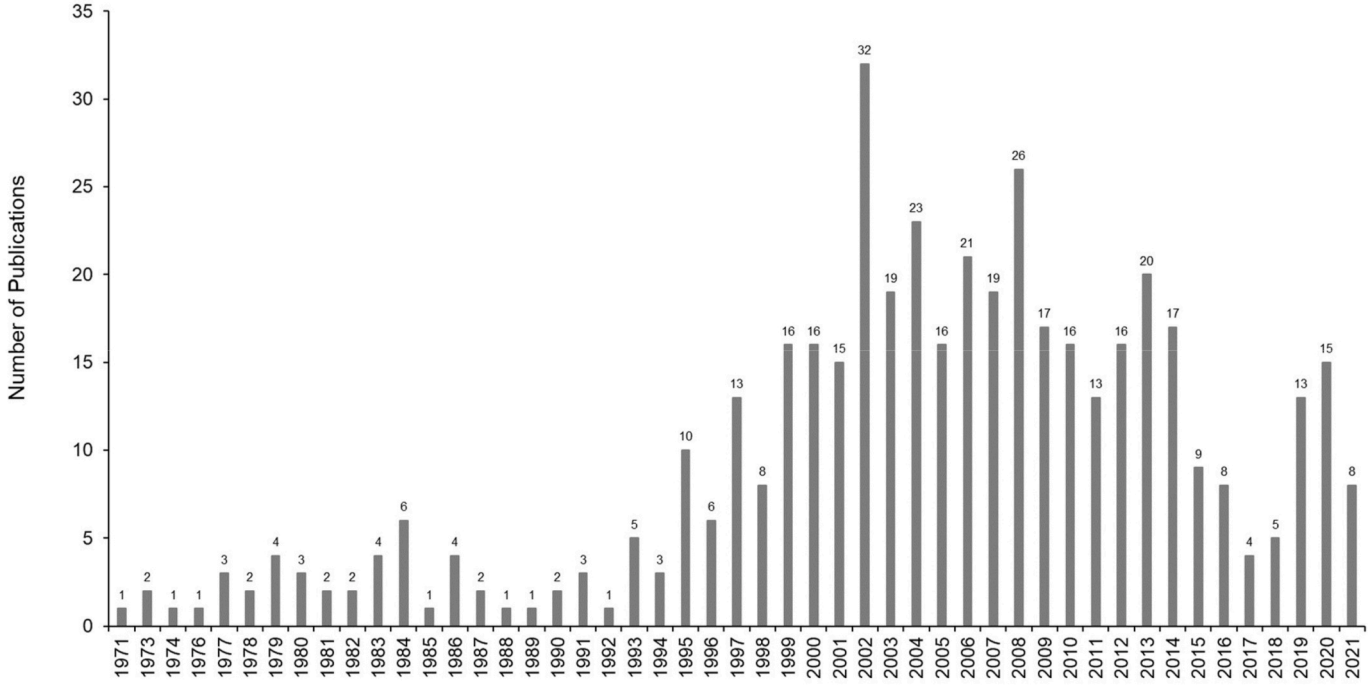


Fig. 1. Trend in the annual publication output on *Prunus africana* research from 1971 to 2021.

complexities stemming from national and international policies that restrict access to plant material for research and secondly, due to political instability and turmoil in some areas where *P. africana* grows. In Cameroon, for example, since 2017 and 2019, violent conflict between government security forces and Anglophone separatists centred around *P. africana* growing areas of south-west and north-west Cameroon, displacing 430000 people (Matfess, 2019). While long-running conflicts in Burundi (Ngaruko and Nkurunziza, 2000; Serwat, 2020) and the DRC (Autesserre, 2008; Mathys and Vlassenroot, 2016) have placed significant barriers in the way of field research (particularly in the eastern DRC).

The World map, showing the contribution of countries towards *P. africana* research, is illustrated in Fig. 2. The colour-coded legend reflects the number of publications; the United States of America (USA) is identified as the key contributor, with 105 publications. France ranks second with 57 co-authored publications, while Germany (45), Italy (40), the United Kingdom (UK) (39), and Kenya (36) follow in the next colour category. It was interesting to observe that even though *P. africana* is endemic to Africa and Madagascar, only a few African countries have been actively involved in the research, and these include Kenya (output = 36), Ethiopia (24), South Africa (18), and Cameroon (17). Other countries indicated in the light green colour have made a minimal contribution to this area of research, with fewer than 10 publications each. We suggest that this geographic distribution of research outputs on *P. africana* has been determined by three main factors. Firstly, a growing number of studies in Europe, after *P. africana* extracts were commercialised by a French company in the 1970's, followed by other companies in Europe. Secondly, research support for studies of herbal treatments for BPH in North America and Europe, where BPH is a widespread ailment amongst older men. The occurrence of saw palmetto (*Serenoa repens* Bartram J.K. Small) in the USA, which is also used to treat BPH (Tacklind et al., 2009) may also have stimulated comparative studies between *S. repens* and *P. africana.* Thirdly, since the 1990s, international funding of joint research with African scientists to support research on *P. africana* conservation, agroforestry, and genetics.

The network country map (Fig. 3) shows collaborative linkages between countries contributing towards *P. africana* research. In this plot, countries are linked by their cumulative co-authorship, and the size of a node indicates total collaborative strength. The number of networks on a node indicates the size of the collaborative environment of a particular country, while the thickness of a link indicates co-authorship strength between the countries. From the plot, seven collaborative clusters are clearly visible as indicated by the different colours (Fig. 3). Considering the nodule size, the top six countries in establishing collaborative networks are Kenya (total link strength = 41), Germany (36), USA (29), Uganda (29), Cameroon (28), and Italy (24).

The red cluster comprises mostly the African research community, where research on *P. africana* trade, conservation, genetics, and agroforestry potential came from three main international sources of funding. Initially, through the WWF/UNESCO/RBG Kew "People and Plants Initiative" which supported the work in Cambronero et al. (2022) that led to CITES Appendix II listing of *P. africana* in 1994. Followed by funding through the CGIAR's World Agroforestry Centre (ICRAF) based in Nairobi, Kenya, which supported research through ICRAF offices in Cameroon, Madagascar, and Zimbabwe. Then a series of studies funded through the Austrian Development Agency (ADA) in partnership with the CGIAR (Biodiversity International) and studies supported by the Centre for International Forestry Research (CIFOR). The green cluster with the UK at the core, shows close collaborations with the Netherlands, Spain, and Australia. Germany, with a high linkage strength, collaborations with Finland and China, while Belgium, Italy, France, and Poland have a larger network. Similar to the Ugandan and Ethiopian clusters, the USA has a low linkage strength. However, despite few collaborative networks, the research output for the USA is the highest, at 105 publications. The network country map provides a clear outline of the *P. africana* research communities where networks can be improved to include more linkages with African countries that harbour this important indigenous species.

The most frequently occurring terms used in *P. africana* publications were observed through the construction of a term co-occurrence map (Fig. 4). The term map shows four prominent clusters, with the red cluster on the right-side comprising terms related to ecology, propagation, conservation, and sustainability. The separation of the red cluster from the others indicates that these publications focussed acutely on ecological aspects. Although some chemical profiling, composition and variation studies were conducted, there was little integration with topics

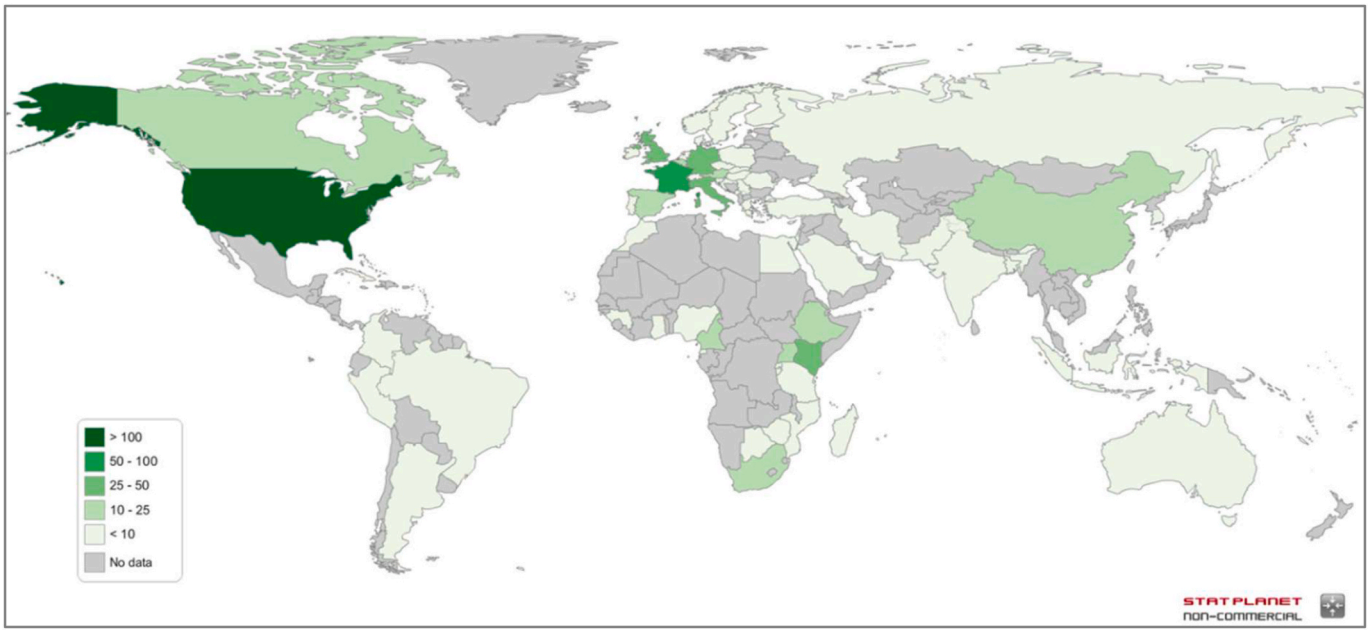


Fig. 2. Global contribution towards *Prunus africana* research over the period 1971–2021. The world map shows the publication output for each country which is indicated by the colour intensity, where the darker the colour, the higher the publication output and *vice-versa.* (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

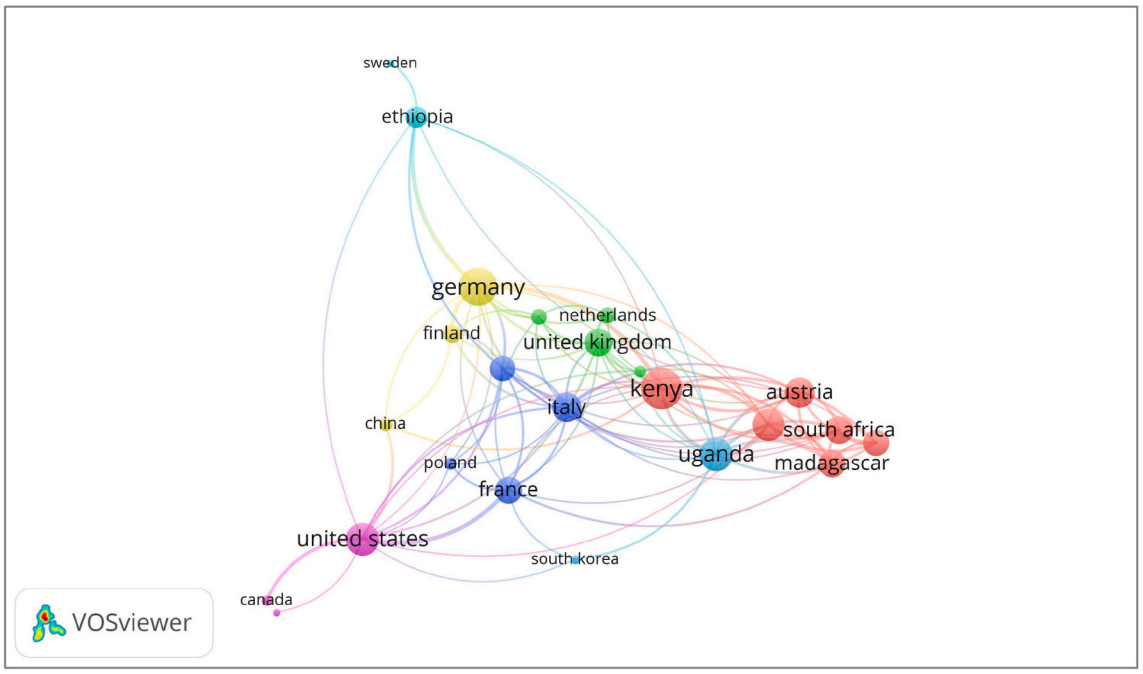


Fig. 3. Network country map showing collaborations between countries contributing towards *Prunus africana* research. Countries with the same colour indicate co-authorship, the size of a node indicates total collaborative strength and number of networks on a node indicates the size of the collaborative environment of a particular country. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

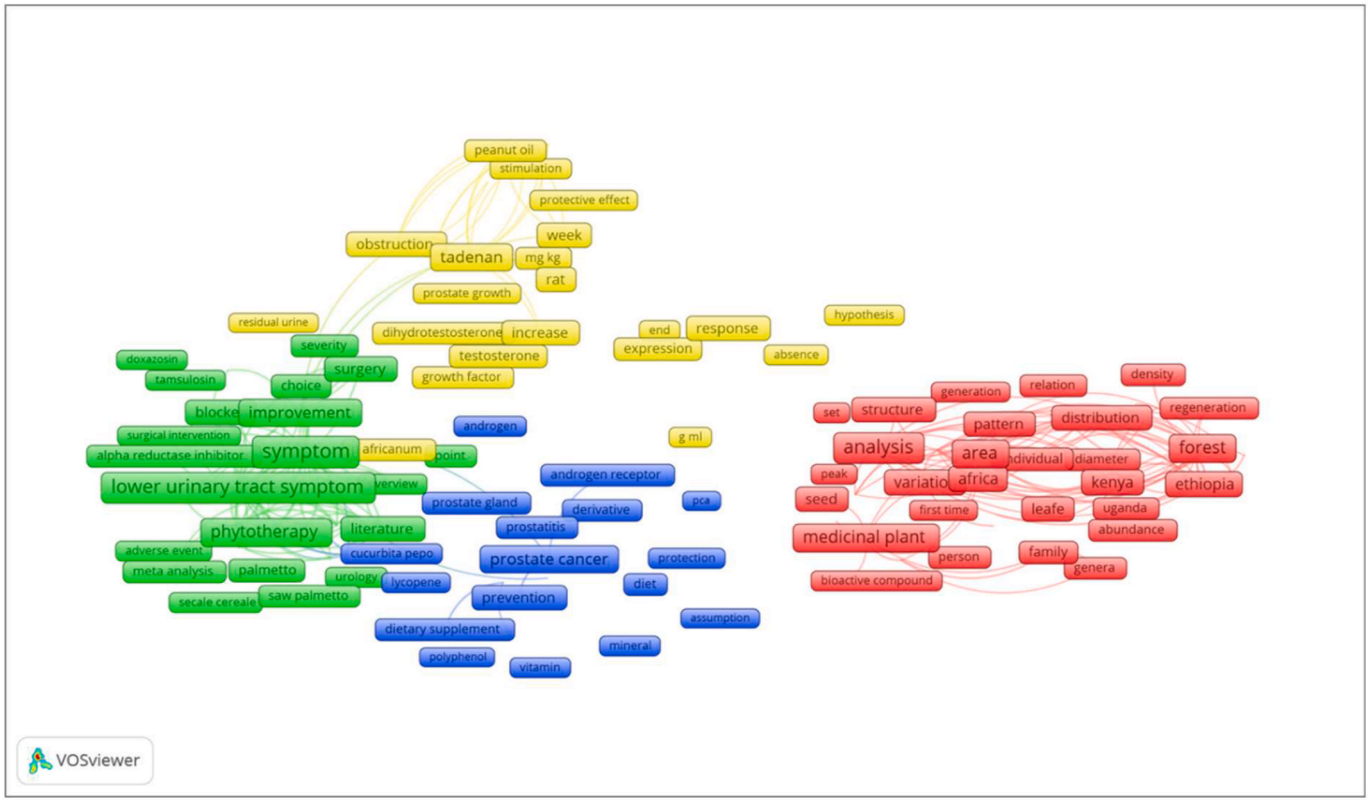


Fig. 4. Term co-occurrence map for *Prunus africana* research based on the abstract and keywords. Colours indicate clusters of related terms highlighting the topics/subjects covered in the publications. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

on the left side. The three clusters on the left of the term map demonstrate close linkage of the research through bioactivity assessment of *Prunus,* in relation to BPH, prostate cancer and urinary tract infections (UTIs). A closer analysis of the data revealed that the yellow cluster predominantly describes *in vivo* animal investigations of pharmaceutical and phytotherapeutic interventions for conditions related to the prostate. The green and blue clusters are characterised by clinical research on BPH, prostate cancer and the urinary tract system. Reviews and meta-

analysis studies on phytotherapies for these conditions also form a major part of these two clusters. A closer inspection of the abstracts revealed that reviews form a significant component of the publications and that the majority of the studies conducted were clinical trials.

Table 1 is a list of the journals carrying most of the publications on *Prunus*, ranked based on the output. Urology and phytotherapy are the top two of the hot topics in research on *P. africana*, followed by studies on *P. africana* population biology (distribution, ecology, and genetics). The top journals carrying 10 papers each are Journal of Urology and Journal of Ethnopharmacology with total citation counts of 463 and 384, respectively. Although the European Urology Journal had a moderate number of publications (6), it garnered 328 citations, which is indicative of the impact of the manuscripts the journal carries. The data indicates that *P. africana* is one of the few African plants that boasts many clinical papers in high impact journals.

4. Botanical aspects

4.1. Description and classification

Prunus africana (Rosaceae) (Fig. 5) is a forest canopy tree that is characterised by multiple branches and a spherical crown and reaches a height of 30–45 m (Letouzey, 1978). The trunk can have a diameter of 1 m at maturity and is covered with blackish-brown, fissured bark on mature trees (Fig. 5A and E) and smoother bark with prominent lenticels on younger trees (Fig. 5G) (Kalkman, 1966; Hall et al., 2000; Stewart, 2003). The shiny leaves are simple, alternative with finely toothed margins and have an elliptic shape. They are deep green on the upper side and lighter on the underside (Fig. 5C). The petioles are deep pink, and the midribs are 5–15 cm long. Small, bisexual, fragrant, greenish, or whitish-cream flowers are borne solitary or occur in branched axillary sprays of 3–7 cm in length (Fig. 5B). The fruits (typically 7 mm long, 1.3 cm wide) are spherical, fleshy, drupaceous, pinkish-brown and bi-lobed, with thin, dark red to reddish-brown pulp when ripe, and bitter in taste (Fig. 5C). The bark is commercially harvested in large quantities or in smaller amounts for local traditional medicine. Commercial harvesters tie slabs of bark into bundles for easier transport (Kalkman, 1966; Cunningham and Mbenkum, 1993; Fraser et al., 1996; Stewart, 2003; Komakech et al., 2017). When crushed, the leaves, twigs, fruits, and bark give off the scent of cyanide, due to cyanogenic glycosides produced by the plant (Kalkman, 1966; Fraser et al., 1996). The reddish mature fruits are dispersed by birds and some primates (Cunningham and Mbenkum, 1993). The cyanogenic glycoside rich leaves are eaten by the red, black, and white colobus monkeys as an important source of self-medication (Fashing, 2004).

Prunus is the largest member of the sub-family Amygdaloideae syn. Prunoideae, which includes the widely produced and consumed sweet cherry (*Prunus avium* (L.) L.), peach (*Prunus persica* L.), plum (*Prunus domestica* L.), African cherry (*Prunus africana* (Hook.f.)) and almond (*Prunus dulcis* (Mill.) D.A. Webb). Of these sub-family members, *P. africana* is the only species that is indigenous to Africa and is possibly chemically distinctive (Stewart, 2003). A line diagram of *P. africana* illustrating various salient morphological characteristics is shown in Fig. 6.

Table 1
Ten most productive journals (including impact factors (IF)) with at least five publications on *Prunus africana* from 1971 to 2021.

IF (2020)	Journal Name	Total publications on *Prunus*	Citation count	*h*-index[a]
7.450	Journal of Urology	10	463	8
4.360	Journal of Ethnopharmacology	10	384	8
5.588	BJU International	9	299	6
2.649	Urology	7	186	6
0.875	African Journal of Ecology	7	113	6
20.096	European Urology	6	328	5
3.092	Current Urology Reports	6	99	5
3.240	Plos One	6	130	4
2.030	International Urology and Nephrology	5	78	4
–	Canadian Pharmaceutical Journal	5	9	1

[a] *h*-index indicates the highest number of papers that have had at least the same number of citations.

4.2. Geographical distribution and habitat

Prunus africana occurs in montane forests scattered across sub-Saharan Africa, Madagascar, and some offshore islands (Fig. 7). In West Africa, *P. africana* is restricted to higher altitude forests on oceanic islands along the Cameroon Volcanic Line (CVL), the 1600 km long chain of volcanoes that includes São Tomé and Principe, and Bioko (3008 m asl) in the Gulf of Guinea (Fitton and Dunlop, 1985; Cunningham and Mbenkum, 1993). As a species preferring temperate conditions, *P. africana* rarely occurs below 800 m asl in tropical Africa. This altitudinal limit gets lower as conditions become cooler further away from the equator, so that at the southernmost part of its range (the Bloukrans River, Western Cape, South Africa), *P. africana* grows close to sea level (Geldenhuys, 1981). In Cameroon, *P. africana* is restricted to the mainland montane forest "islands" along the CVL from Mount Cameroon (4095 m asl) on the coast, to Mt. Manengouba (2411 m asl), the Bamboutos massif and the Bamenda highlands (such as Mt. Oku (3011 m asl). *Prunus africana* also occurs in the Afromontane forests of Burundi, Ethiopia, Equatorial Guinea, South-Eastern Nigeria, Rwanda, São Tomé and Principe (Kalkman, 1966; Vivien and Faure, 1985; Cunningham et al., 1997; Hall et al., 2000; World Health Organization, 2002; Gurib-Fakim, 2006). In the Democratic Republic of the Congo (DRC), the species is restricted to the Kivu region. The species also occurs in East and southern Africa: Angola, Eswatini (previously Swaziland), Tanzania, Uganda, Zambia, Mozambique, and Zimbabwe (Fig. 7) (United Nations Environment Programme, 2008).

This species is light demanding and commonly occurs in open stretches on the edges of forests and in areas of disturbed vegetation (Geldenhuys, 1981; Ewusi et al., 1992; Kiama and Kiyiapi, 2001). It occurs at high altitudes (1500–2000 m asl) and prefers average temperatures of 14–18 °C throughout the year, although it can tolerate temperatures of 12–26 °C, in humid and semi-humid tropical areas (Achoudong, 1995; Dorthe, 2003; Bodeker et al., 2014). The tree flourishes in medium to light soils and in a climate with a distinct dry season and an average yearly rainfall of 900–1400 mm, but can tolerate 700–2000 mm (Graham, 1960; Dorthe, 2003). *Prunus africana* can be easily propagated from seed, which can be left to germinate in a well-drained growth medium in trays or in well-prepared seedbeds. When exposed to favourable temperate climatic conditions, *P. africana* is a fast-growing tree, with up to 1 m of growth recorded per year. *Prunus africana* is a natural habitat and nutriment provider for insects, birds, rare primates and for canopy epiphytes, including a variety of mosses, orchids and ferns (Tchouto, 1996). The seed is spread by local animals and birds that eat the fruit (Cunningham and Mbenkum, 1993; Sunderland and Tako, 1999; Stewart, 2003).

Unsustainable harvesting and loss of habitat have contributed to a decline in the geographical distribution of the species. Subsequently, it has been classified as vulnerable on the current International Union for Conservation of Nature (IUCN) Red List of Threatened Species. Fortunately, due to its occurrence over a very large geographical area, it is not under threat of extinction. Although the species is fairly easy to cultivate, this is being done only on a relatively small scale compared to the level of demand. Larger scale cultivation takes place in Cameroon, Kenya, and Uganda (Fig. 8) (Orrego, 2005; FranzeL et al., 2014; Cunningham et al., 2016).

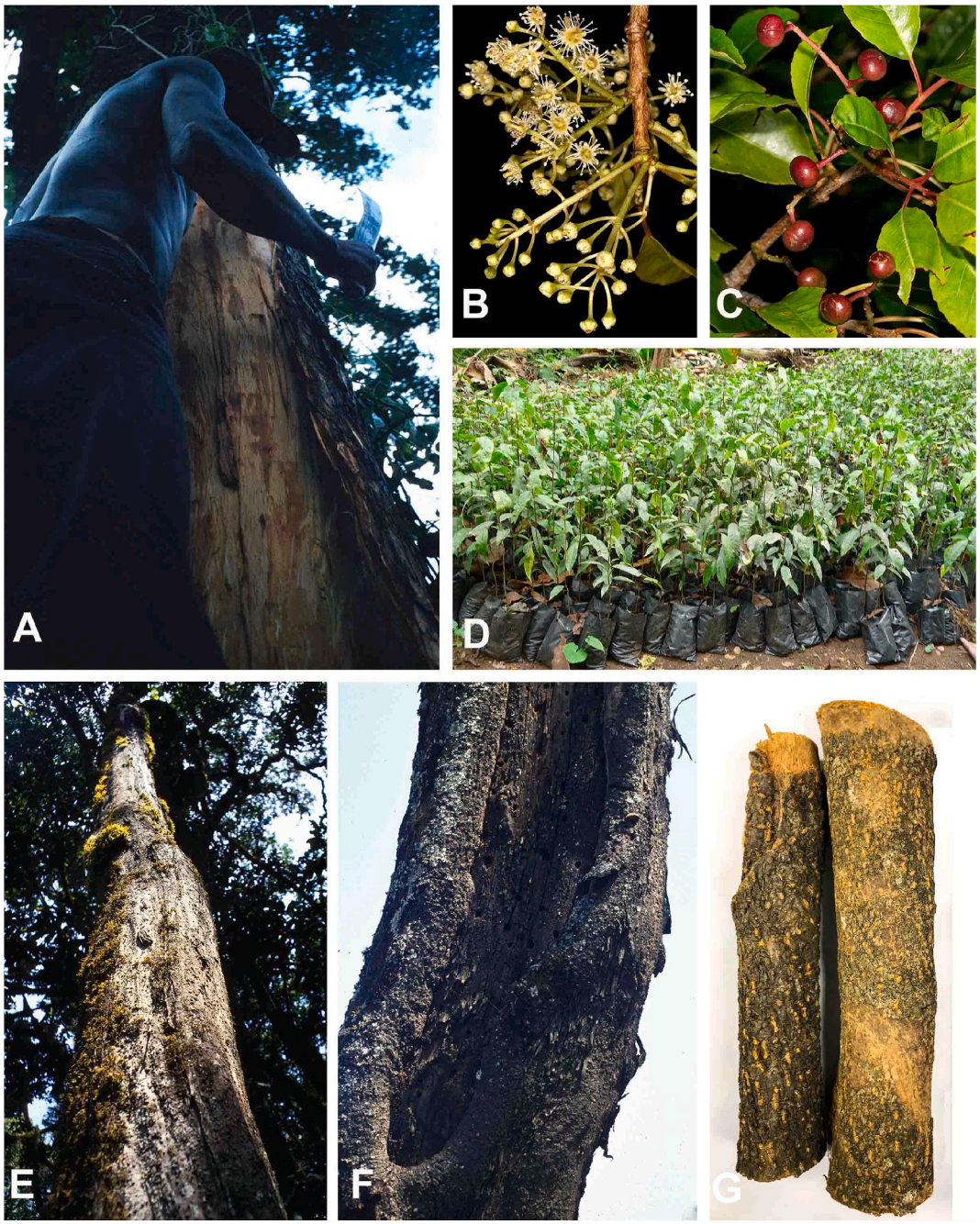


Fig. 5. *Prunus africana*: commercial wild harvest and wild collected seedlings. A commercial bark harvester debarking a large *P. africana* (Bamenda highlands, Cameroon (A), *P. africana* flowers (B), *P. africana* fruits (C), wildings collected and transplanted into a small nursery used by local farmers (Mt. Cameroon) (D), bark recovery after commercial debarking in intact, moist forest. Moss is growing on the original intact bark (E), failed bark regrowth and wood borer (Cerambycidae) attack into a *P. africana* trunk in an exposed site (Dschang area, Cameroon) (F) and smoother bark from younger *P. africana* (G). [Photos: A & D-G by Cunningham, A. B. and B, C by Van Wyk, A-E.].

The Community Action for Development (CAD), a non-profit organisation, initiated a project aimed at promoting the domestication of *P. africana* within existing farming systems and woodlots since 2012 in the Kupe Manenguba Division (Cameroon). The organisation sought to protect the species through direct regeneration, environmental education and encouraging responsible harvesting practices (CAD, 2013).

4.3. Sustainability, cultivation and ecological impact of the trade in *Prunus africana* bark

There is great variation in the resilience of different tree species in their ability to recover from, and regenerate bark, after extensive damage (Cunningham, 2014a,b; Yemata and Haregewoien, 2022). *Prunus africana*, *Warburgia salutaris,* and some of the latex-producing *Ficus* species (such as *Ficus natalensis*) are examples of a few resilient African tree species that are able to regrow their bark completely and may even recover after complete removal of the bark (Cunningham, 1991, 2014). The ability of *P. africana* to regrow damaged bark confers some resilience, but in practice, the sustainable harvesting of *P. africana* bark has proved to be unrealistic, due to harvesting rules not being followed, with complete girdling of many trees (rather than partial debarking) and poor regrowth and wood borer attack on trees in dry

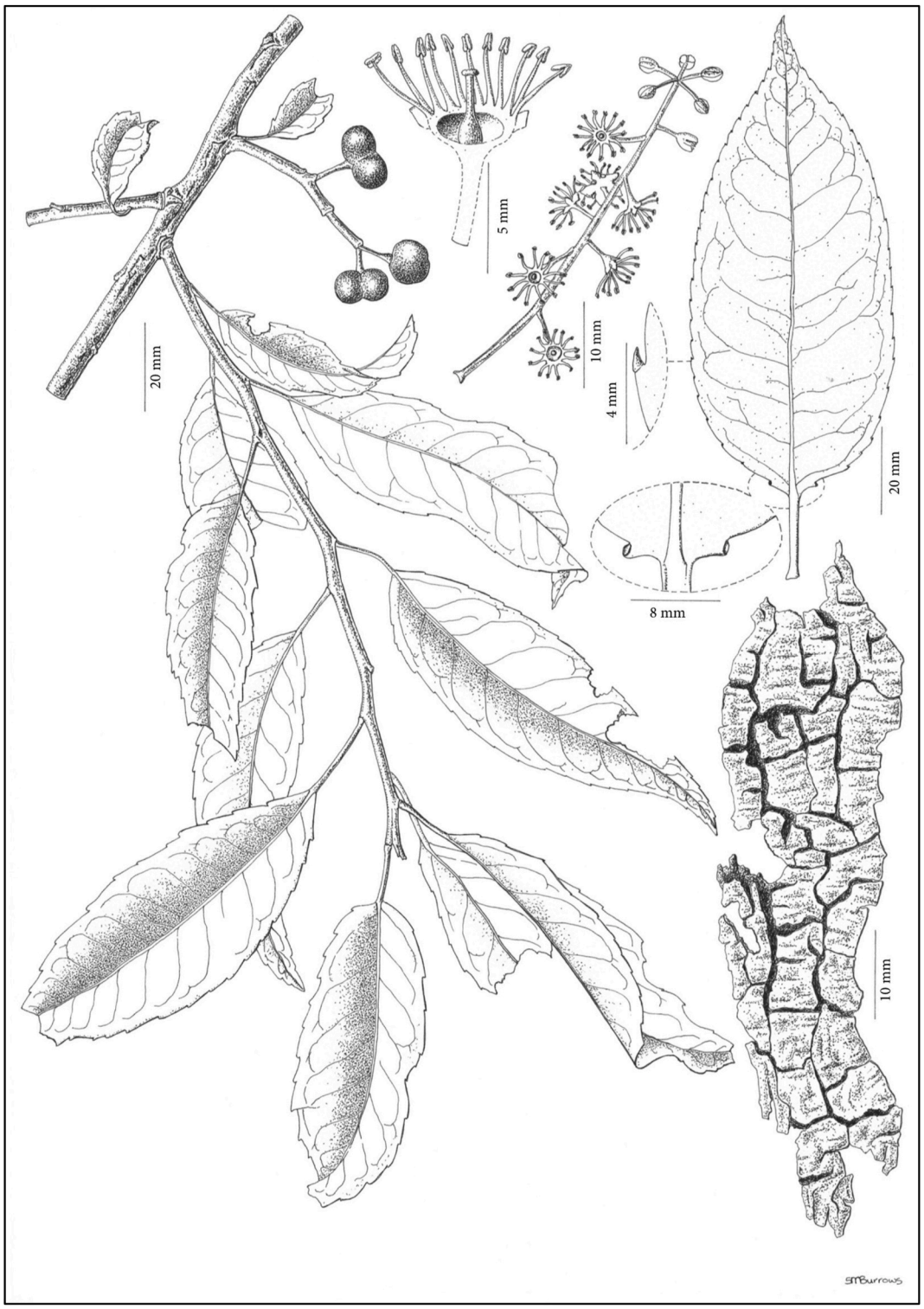


Fig. 6. Botanical illustration of *Prunus africana* showing distinct morphological features.

sites (Cunningham and Mbenkum, 1993; Cunningham et al., 2016).

Wild-harvested *P. africana* bark from Africa and Madagascar has been internationally traded to a greater extent than any other African medicinal plant resource (Bii et al., 2010; Betti et al., 2019). In 2016, Cameroon exported 658.6 metric tons of *P. africana* bark, representing 72.6% of the international *P. africana* bark trade, a significant increase from an average of 38% over the years 1995–2004. Cameroon is still the main exporting country owing to zero quotas granted by CITES to Burundi, Equatorial Guinea, Kenya, and Madagascar (Fig. 9). In 2012, according to CITES records, Cameroon supplied 72.6% of the global supply of *P. africana* bark (658.7 tonnes), with the remainder coming from Uganda (176.2 tonnes) and the DRC (72 tonnes) (CITES, 2012). A decade later, the CITES quota for *P. africana* bark exports from Cameroon had dropped to 397.86 tonnes (CITES, 2022).[1]

Commercial harvest was initiated in 1972, when the company

[1] Export quotas | CITES (accessed 24 July 2022).

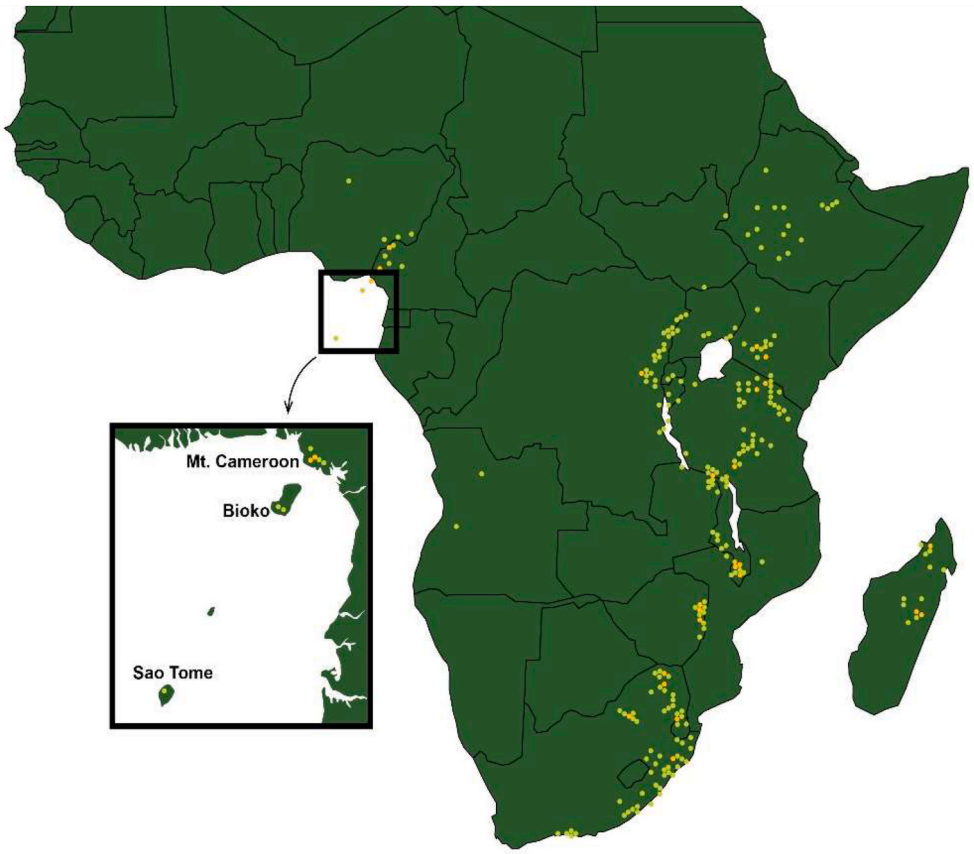


Fig. 7. Geographical distribution map of *Prunus africana* in Africa and Madagascar, including detail showing occurrence in Montane forests on offshore volcanic islands (Bioko (Equatorial Guinea) and São Tomé (São Tomé and Principe)).

Plantecam Medicam (later Plantecam) began harvesting in the north-western and western provinces, under regulations guiding harvesting practices (Cunningham et al., 2016). Opportunistic commercial exploitation by Cameroonian entrepreneurs from the 1980s ensued when Plantecam lost their monopoly on bark harvest. Resulting in resource depletion (Cunningham and Mbenkum, 1993; Stewart, 2003). Over-exploitation has also occurred in Madagascar, where regulations do not specify a minimum size tree as in Cameroon (>30 cm diameter at breast height (DBH)) (Neimark, 2010). Neither was the forestry rule of two trees per hectare to be retained as a seed source, not adhered to in Madagascar (Dawson, 1998). In Kenya, *P. africana* grows in moist forested areas above altitudes of 1500 m (Hall et al., 2000). The bark is primarily harvested from trees growing in privately owned forest land being cleared for tea plantations and resettlement. No harvesting is permitted in protected areas (Cunningham et al., 1997). Harvesting in Kenya started in 1995 with the export of 150 tons of bark, which reached a peak of 500 tons in 1998, and then declined to about 300 tons in 2000 (Nyamai et al., 2015), followed by a ban on exports from Kenya.

In South Africa, where *P. africana* has a limited distribution, harvesting occurs for the commercial trade in traditional medicines (Cunningham, 1988). The leaves of *P. africana* have been investigated as a source of active compounds for potential marketing. Although the leaves are reported to contain lower concentrations of the desired active compounds, they may be a viable alternative to the use of bark, particularly if trees can be pruned to a height that provides easy access for harvesting. The majority of harvested bark is exported to Europe and the USA, a growing market, but a shift of a significant proportion of the market to China and India has occurred in the first decade of this century (Cunningham, 2014a,b). A number of policies, both at the national and international level, have been adopted to address the challenge of sustainable harvesting of medicinal species for their health benefits. In this regard, *P. africana* is included in the IUCN Red List of Threatened Species, listed as "vulnerable,'' it was included in Appendix II of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) at the 9th CITES Conference of the Parties in 1995. Cameroon, Madagascar, Kenya, Tanzania, and the Congo are the main suppliers of globally traded *Prunus*. In 2012, Cameroon was the source of most of the traded bark (72.6% equivalent to 658.7 metric tons), due to a ban on quotas by CITES on material from Burundi, Equatorial Guinea, Kenya, and Madagascar (Uganda supplied an additional 176.2 tons, while 72 tons were sourced from the Democratic Republic of the Congo) (Stewart, 2009; Cunningham et al., 2016). The bark export trade from Africa was estimated at 3200–4900 metric tons per year in 1998, compared to only 10 metric tons in 1976 (Schippmann, 2001).

Mismanagement and depletion of wild *P. africana* populations in Burundi, Cameroon, Equatorial Guinea, and Madagascar has been driven by a combination of commercial over-harvesting of wild populations and corruption within the supply chain (Sunderland and Tako, 1999; Neimark, 2010; Cunningham et al., 2016). Cultivation of the trees is the obvious solution to protect the species and ensure a constant supply to the world market. Since *P. africana* is a light tolerant and easily propagated secondary forest species, it is well suited for reforestation, as boundary markers, or for the establishment of plantations (Cunningham and Mbenkum, 1993; Franzel et al., 2014; Komakech et al., 2020). In Cameroon, trees have been successfully propagated from cuttings, with 10% of cuttings establishing roots within 3 weeks in a sand medium and in the absence of rooting hormone. The application of auxin-based rooting hormones is associated with an increased root-strike rate and could be applied to cuttings. More than 35 years ago, Leakey (1987) emphasised the advantages of clonal forestry in terms of improving the yield and quality of forest products, and the benefits of its implementation in tropical regions. With the potential to select *P. africana*



Fig. 8. Plantation trials and agroforestry production of *P. africana*. A remnant of a *P. africana* plantation trial started in Kenya over 100 years ago (in 1919) (A), *P. africana* growing in an agroforestry system in South-Western Uganda as part of Plan VIVO's carbon credits project (B), a local farmer near Mt. Cameroon with a tagged *P. africana* grown as a coffee shade tree (C) and *P. africana* in a multi-species agroforestry system (Bamenda highlands, Cameroon) (D) [Photos: A, C, D by Cunningham, A.B. and B by Stevens, A.]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

chemotypes that produce high yields of active compounds. To some degree, these skills already exist in Cameroon, and timber trees are mass-produced in low-technology propagators (Tchoundjeu et al., 2002.). The success of this approach is reflected by the more than 1,610, 000 *P. africana* trees that were planted in high-altitude regions of Cameroon over a period of 30 years (1976–2007). The regeneration of *Prunus* stocks and the preservation of genetic diversity are crucial in ensuring the highest quality of active compounds (Bodeker et al., 2014).

The International Centre for Research in Agroforestry (ICRAF) and the cultivation programme at the Limbe Botanic Garden were at the forefront of cultivation efforts in Kenya and Cameroon, respectively. Cunningham and Mbenkum (1993) suggested the planting of *P. africana* at low altitudes, particularly in areas where palm oil plantations were abandoned. Unfortunately, the susceptibility of *P. africana* to wood borer infestation and to infection by fungal pathogens is increased at low altitudes and could result in lower timber value (Cunningham et al., 2002). The land is scarce at higher altitudes, particularly in Cameroon where most land outside of forest preserves has been utilised for crop farming or pasture. Cultivation and management programmes have been established to protect wild populations and preserve genetic resources. These initiatives include new enrichment plantings, plantations, and farm production on a small scale, as well as the formulation of new regulations to preserve the species (Bodeker et al., 2014).

5. Ethnopharmacology and other uses

Prunus africana is still an important component of African Traditional Medicine. The species was reported as the fourth most widely used medicinal plant species in the Mount Cameroon region of Cameroon and was collected by 14% of the households according to a survey published by Watts and Akogo (1994). Noumi (2010) reported that *P. africana* is a major ethnomedicine used in the treatment of prostatic disease in Foumban, Cameroon. Both leaves and roots are relied on for the treatment of a variety of unrelated conditions that include fever, stomachache, urinary tract infection, gonorrhoea, kidney disease and heart infections (Sunderland and Nkefor, 1997; Stewart, 2003), as well as for veterinary applications (Ingram et al., 2009). Simbo (2010) in his study, discovered that traditional healers and communities in Babungo, Northwest region, Cameroon, use *P. africana* to treat wounds and burns. The crushed, dry bark is used to prepare a decoction or infusion in most cases (Stewart, 2003; Komakech and Kang, 2019). Jiofack et al. (2008, 2009) discovered that the decoction of *P. africana* bark is used to treat heartburn and gastralgia in a survey on the ethnobotanical uses of medicinal plants in Cameroon's south-west ethnoecological region. In East Africa, water is added to the pounded bark, and the infusion is taken to treat stomach ache, and as a purgative for cattle in veterinary medicine (Kokwaro, 1976). The Nandi community in Kenya use *P. africana* for the treatment of diabetes, stomach problems, high blood pressure, and



Fig. 9. The *P. africana* supply chain in Cameroon, which for decades has been the major exporter of bark (mainly to Europe). Bark is carried out of the forest (A), a typical bundle of *P. africana* bark (B), *P. africana* bark stored at the former Plantecam factory at Mutengene (Cameroon), which is now closed (C), a machine bought through a development aid attempt to add value for a harvester co-operative (D) and final products produced in Europe (E and F) [Photos by Cunningham, A. B.].

adverse skin conditions (Ngule et al., 2014; Koros et al., 2016). In central Kenya, the Kikuyu community use tree parts for the treatment and management of malaria (Njoroge and Bussmann, 2006). According to a study conducted by López and Shanley (2014), *P. africana* is used in traditional medicine to treat malaria and other related conditions. A survey in the Meru District of Kenya revealed that a decoction or infusion prepared from powdered stem-bark is also a well-known treatment for malaria (Muthaura et al., 2007). According to an ethnomedicinal study conducted by Amri and Kisangau (2012), the bark decoction of *P. africana* is used to treat stomachache in villages near the Kimboza Forest Reserve in Morogoro, Tanzania. The bark is indigenously used as a laxative and for "old men's disease", which translates to difficulty in passing urine (Pomatto, 2001; Abera, 2014). In Uganda, *Prunus* is used to treat many ailments associated with pain and inflammation (Stewart, 2003; Komakech and Kang, 2019). Ochwang'i et al. (2014) listed *P. africana* as one of the most highly sought-after medicinal plants for the treatment and management of cancer in the Kakamega County of Kenya. Bark extracts have been found to improve urologic symptoms in prostate cancer patients, due to their apoptotic and antiproliferative effect on the prostate (Kadu et al., 2012; Jena et al., 2016).

In southern Africa, the bark is employed as a treatment for intercostal pain (Pujol, 1990; Komakech et al., 2017). Eldeen et al. (2005) reported on the use of *P. africana* decoction in the treatment of stomachache and other diseases in South Africa. In the 1960s, a German physician noted that Zulu men in the Vryheid area of KwaZulu-Natal, South Africa used an infusion of *P. africana* bark to treat micturition, who then realised its beneficial effects in the treatment of BPH and subsequently mentioned this potential to Jacques Debat, the director of the French company Laboratoires Debat. The result was the filing of an early patent, and the beginning of the commercialisation of the product (Cunningham and Mbenkum, 1993). Demand for *P. africana* internationally as a raw material for the pharmaceutical trade in herbal BPH treatments continues. In 2007, it was recorded as the most popular medicine in France to treat symptoms associated with BPH. At least 40 brand-name products were available that contained bark extracts of *P. africana* as a main active ingredient. These products were sold globally *via* the internet (Pomatto, 2001; Wittemyer et al., 2008). Tadenan®, a product of Fournier Laboratory, France, and Pygenil®, produced by Indena Spa., Italy, were the most popular pharmaceutical brands containing *P. africana* at the start of the twenty-first century (Cunningham et al., 2002). The distribution and ethnobotanical uses of *P. africana* in Africa are summarised in Table 2.

6. Phytochemistry

Several phytochemical studies have resulted in the isolation of a multitude of secondary metabolites from *P. africana*, including phytosterols, phenols, triterpenes, fatty acids, and long-chain fatty alcohols (Catalano et al., 1984; Bombardelli and Morazzoni, 1997). The chemical structures of selected compounds isolated from *P. africana* are shown in Fig. 10. The first compounds (phytosterols) isolated from a chloroform extract of *P. africana* were 3-β-sitosterol [**1**], 3-β-sitostenone [**2**], and 3-β-sitosterol-glucoside [**3**] (Longo and Tira, 1981). These compounds were reported to curb prostaglandin production in the prostate, thereby mitigating the inflammatory symptoms associated with BPH and chronic prostatitis (Longo and Tira, 1981; Hass et al., 1999; Jimu, 2011; Nyamai et al., 2015). Longo and Tira (1981) isolated pentacyclic triterpenoids, such as oleanolic acid [**14**] from chloroform bark extracts. Catalano et al. (1984) isolated additional and some new constituents, which included ursolic acid [**4**], friedelin [**5**], maslinic acid [**6**], epimaslinic

Table 2
Distribution and ethnobotanical uses of *Prunus africana* in Africa.

Country/Area	Part used	Traditional use	References
Cameroon	Branches	Tool (axe, hoe) handles	Stewart (2001); Cunningham and Mbenkum (1993); Focho et al. (2009)
		Ceremonial spear handles	Stewart (2001)
	Timber	Roof support	Stewart (2001)
		Bridge decks	
		Fuel wood	
		Window and door frames	
	Bark	Traditional medicine (45 human ailments)	Stewart (2001); Cunningham and Mbenkum (1993); Focho et al. (2009)
Kilum-Ijim	Bark	Traditional medicine (11 ailments of domestic animals)	Stewart (2001)
		gastrointestinal disturbances, malaria, and fever	Focho et al. (2009)
	Leaves	Traditional medicine	Stewart (2001)
	Fruit and leaves	Wildlife food	Stewart (2001); Cunningham and Mbenkum (1993)
	Seeds	Traditional medicine (rare use)	Stewart (2001)
Oku	Flowers	Honey production	Stewart (2001)
	Woods/dry wood	Handles of hoes and other tools, as well as fuel for cooking	Stewart (2003)
Uganda	Timber	Beehives supports	Cunningham (1991)
		Beer boats	Lambert (1998)
		Pitsawn lumber	
		Building poles	
		Bean stakes	
		Firewood, charcoal	
		Furniture, flooring, paneling, carving	
		Posts	
		Utensils	
Kenya	Timber	House building and furniture	Beentje (1994)
		railway sleepers	Cunningham and Mbenkum (1993)
		Traditional medicine (fever)	Kokwaro (1976)
		Traditional medicine (gonorrhoea)	Lindsay (1978)
		Traditional medicine (purgative)	Beentje (1994)
	Leaves	Traditional medicine (stomach pain)	Kokwaro (1976)
	Bark	Traditional medicine (purgative)	Beentje (1994)
South Africa	Bark	Traditional medicine (chest pain)	Van Wyk et al. (1997)
		Traditional medicine (intercostal pain)	Hutchings et al. (1996)
	Timber	Wagons	Palmer and Pitman (1972)
East Africa	Leaves	Traditional medicine (stomach pain)	Glover et al. (1966)
West Africa	Timber	Truck bodies	Howe and Westley (1986)
		Chopping blocks	
		Bridge decks	
		Cabinets and furniture	
Dem. Rep. Congo/ Burundi	Leaves	Traditional medicine (insanity)	Baerts and Lehmann (1989)
Unspecified	Unspecified	Traditional medicine (stomach pain, fever, cattle purgative)	Kalkman (1966)
		For arrow poison	Kalkman (1966)
		Anti-inflammatory, kidney disease, urinary tract conditions, fever, malaria, wound dressing, appetite stimulant	Stewart (2003)

acid [**7**] and 2α-hydroxyursolic acid [**8**] from the bark extract. Scarpato et al. (1998) reported the isolation of 4-*O*-β-D-glucopyranosyl-(7, 8)-dimethoxyisolariciresinol [**9**] from a butanolic bark extract. The presence of ferulic acid [**10**] and *n*-docosanol [**11**] were reported by Kadu et al. (2012) in the bark extract using gas chromatography coupled to mass spectrometry (GC–MS). Schleich et al. (2006a) isolated atraric acid (methyl-2,4-dihydroxy-3,6-dimethylbenzoate) [**12**], *N*-butylbenzenesulfonamide (NBBS) [**13**] and phenolic compounds from ethanolic and dichloromethane extracts of the stem-bark.

The isolation of nine triterpenic acids from the chloroform bark extract was reported by Fourneau et al. (1996). These are 2α,3α-dihydroxyurs-12-en-28-oic acid [**15**], 2α,3β-dihydroxyurs-12-en-28-oic acid [**16**], 2α,3β-dihydroxyolean-12-en-28-oic acid [**17**], 3β,24-dihydroxyurs-12-en-28-oic acid [**18**], 2α,3α,23-trihydroxyurs-12-en-28-oic acid [**19**], 2α,3α,24-trihydroxyurs-12-en-28-oic acid [**20**], 24-*O*-*trans*--ferulyl-3β-hydroxy-urs-12-en-28-oic acid [**21**], 24-*O*-*cis*-feruly-3β-hydroxy-urs-12-en-28-oic acid [**22**], and 24-*O*-*trans*-ferulyl-2α, 3α-dihydroxy-urs-12-en-28-oic acid [**23**]. Ngule et al. (2014) confirmed the presence of tannins, saponins, flavonoids, terpenoids, glycosides, alkaloids, and phenols in the hydromethanolic extract of bark collected in a natural forest in Nandi County, Kenya. The fatty acids, myristic acid [**24**], palmitic acid [**25**], linoleic acid [**26**], oleic acid [**27**], stearic acid [**28**], arachidonic acid [**29**], behenic acid [**30**], lignoceric acid [**31**], and linolenic acid, were reported from the chloroform bark extract (Hass et al., 1999; Ganzera et al., 1999). Earlier, the presence of nonacosane [**32**] and hentriacontane [**33**] in the chloroform bark extract was reported by Longo and Tira (1981). *n*-Docosyl ferulate [**34**] was determined in extracts and in soft gelatin capsules containing *P. africana* extract from Indena Spa. (Italy) using HPLC analysis (Uberti et al., 1990; You and Cheng, 1997). Recently, Deresa et al. (2022) reported the isolation of four compounds not previously identified in *P. africana*, from a methanolic stem-bark extract, namely benzoic acid [**35**], *p*-hydroxybenzoic acid [**36**], oleanoic acid-3-benzoate [**37**], and oleanoic acid-22-benzoate [**38**].

7. Biological activities

A wide range of biological effects has been confirmed for extracts and

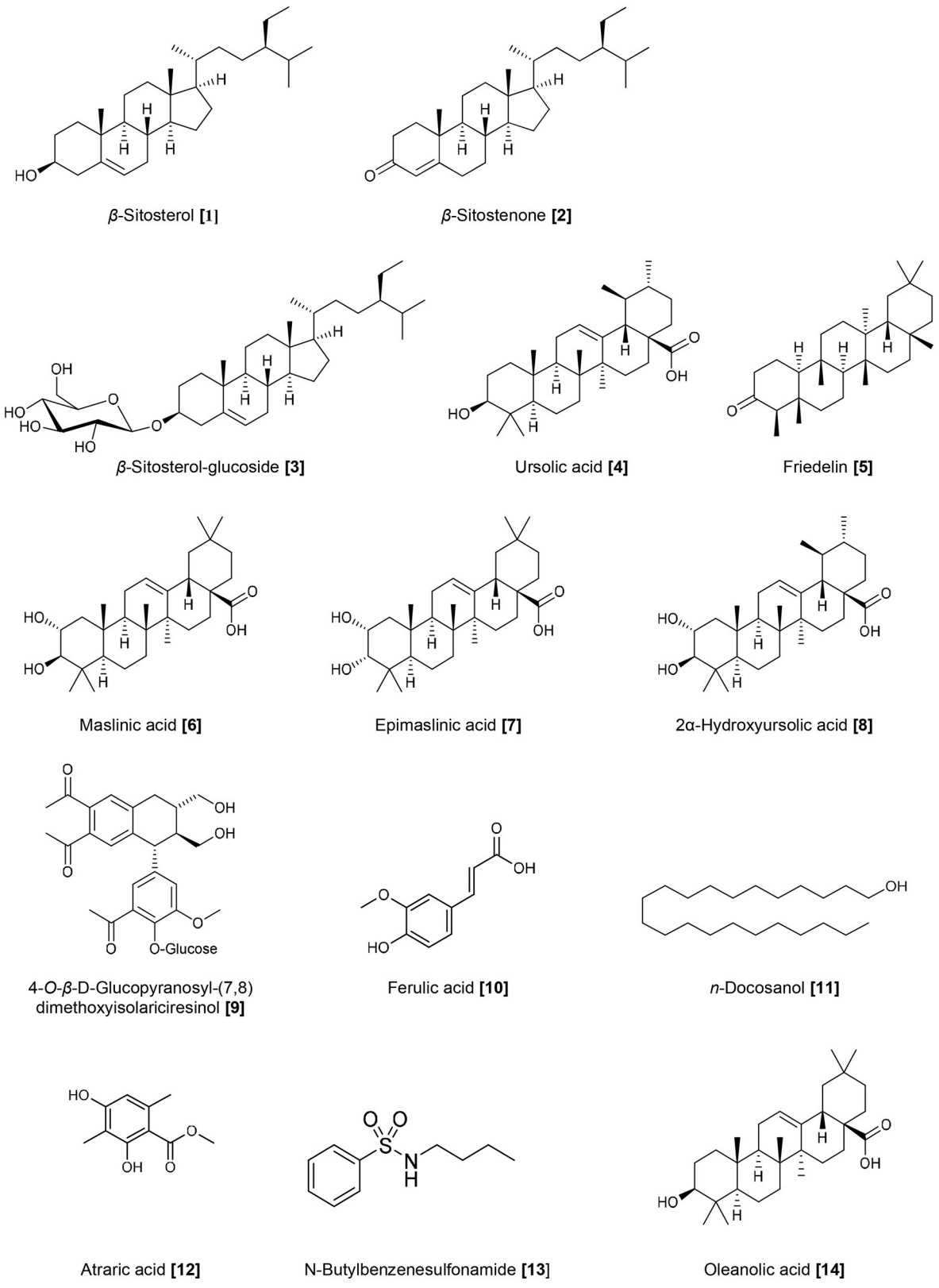
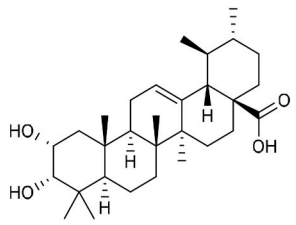


Fig. 10. Chemical structures of selected compounds isolated and identified from *Prunus africana*.

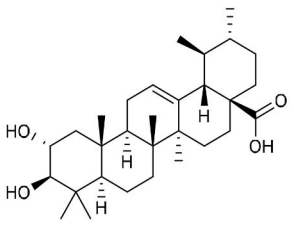
purified compounds from *P. africana* including anti-inflammatory, antimicrobial, anti-oxidant, antiviral, antimutagenic, antiproliferative, anti-asthmatic, and anti-androgenic activities.

7.1. Anti-inflammatory and analgesic activities

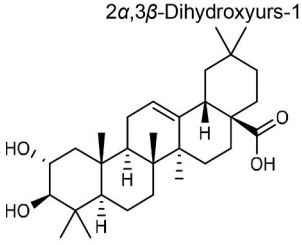
Inflammation is a local response of living tissues to an injury or any irritant substance. Chloroform bark preparations of *P. africana* have



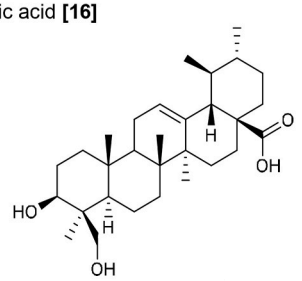
2α,3α-Dihydroxyurs-12-en-28-oic acid **[15]**



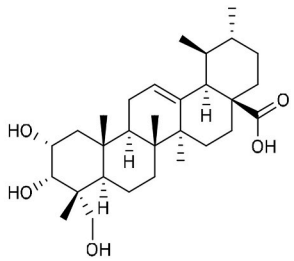
2α,3β-Dihydroxyurs-12-en-28-oic acid **[16]**



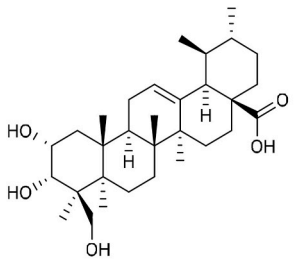
2α,3β-Dihydroxyolean-12-en-28-oic acid **[17]**



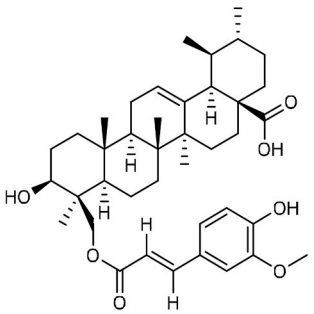
3β,24-Dihydroxyurs-12-en-28-oic acid **[18]**



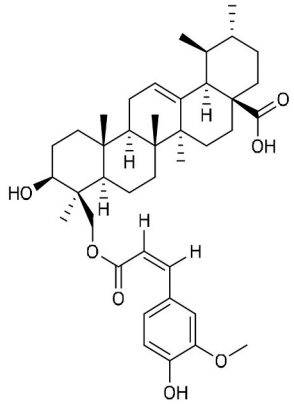
2α,3α,23-Trihydroxyurs-12-en-28-oic acid **[19]**



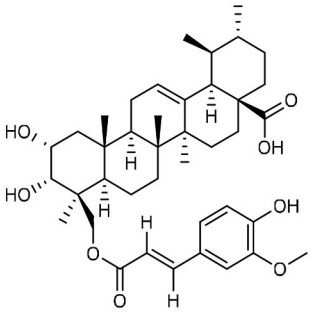
2α,3α,24-Trihydroxyurs-12-en-28-oic acid **[20]**



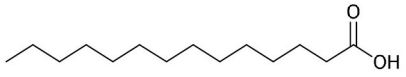
24-*O-trans*-ferulyl-3β-hydroxy-urs-12-en-28-oic acid **[21]**



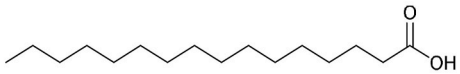
24-O-cis-Feruly-3β-hydroxy-urs-12-en-28-oic acid **[22]**



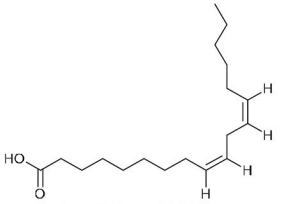
24-O-trans-Ferulyl-2α,3α-dihydroxy-urs-12-en-28-oic acid **[23]**



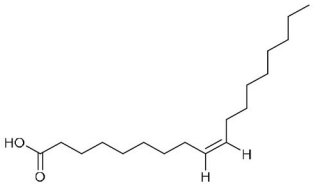
Myristic acid **[24]**



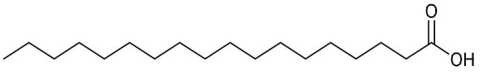
Palmitic acid [**25**]



Linoleic acid **[26]**



Oleic acid **[27]**



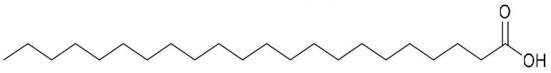


Fig. 10. (*continued*).

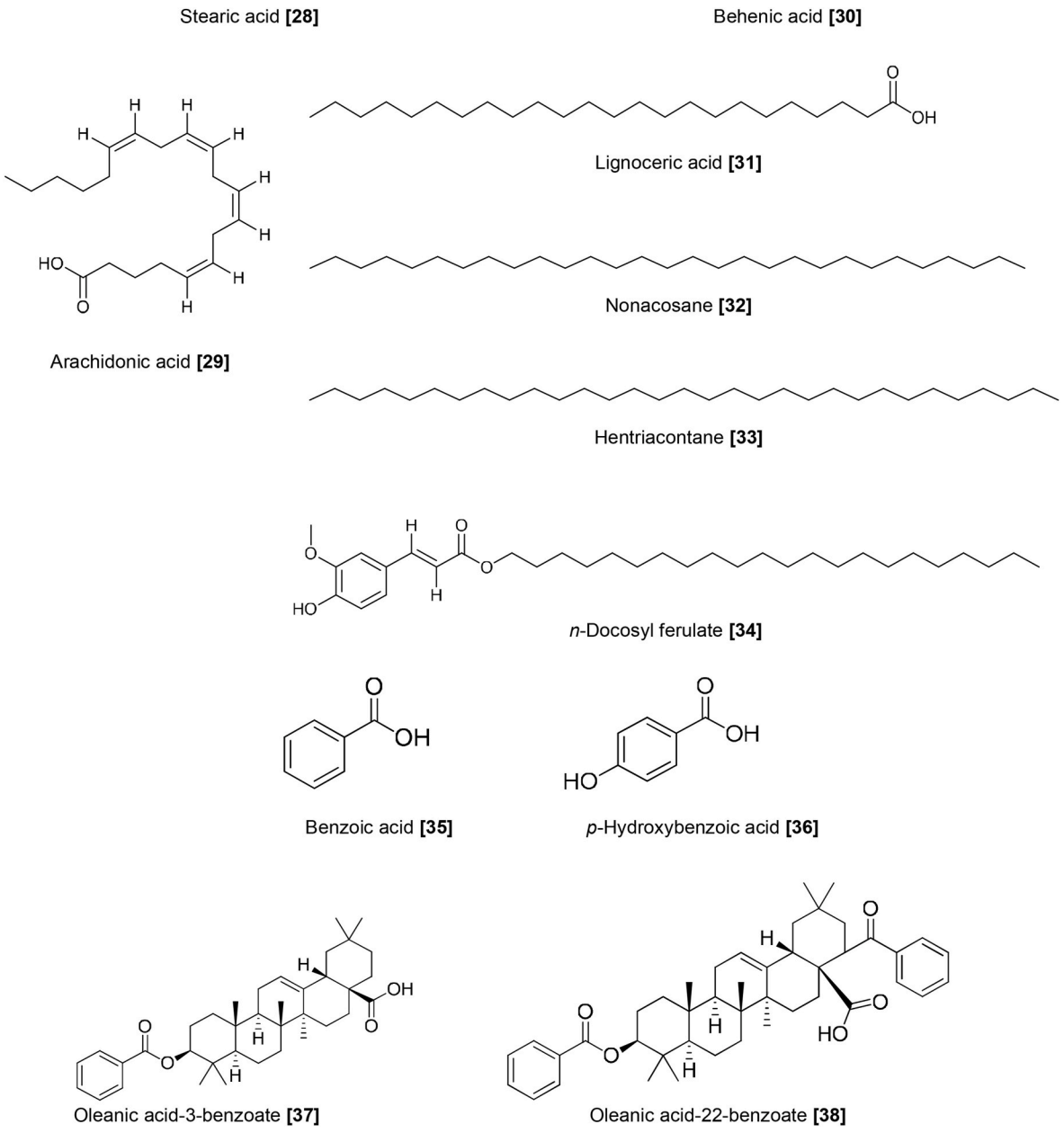


Fig. 10. (*continued*).

reportedly displayed anti-inflammatory effects in the treatment of symptoms associated with mild to moderate BPH. In 1986, Bauer demonstrated that phytosterols, mainly β-sitosterol and β-sitostenone, isolated from *P. africana*, exhibited anti-inflammatory effects by inhibiting the synthesis of prostaglandins. Of great interest was the finding that the activity of the enzyme, 5-α-reductase which is responsible for the conversion of testosterone to dihydrotestosterone (DHT) was inhibited, impeding the primary mechanism responsible for prostate enlargement and the pathogenesis of BPH (Steers, 2001). Various research groups have confirmed the efficacy of the dichloromethane bark extract in suppressing lower urinary tract symptoms, by decreasing inflammation through inhibition of 5-α-reductase in patients with BPH (Andro and Riffaud, 1995; Ishani et al., 2000; Capasso et al., 2003). Lauric acid inhibits the 5-α-reductase enzyme, preventing testosterone conversion to dihydrotestosterone and thus preventing testosterone prostate cancer (Niederprüm et al., 1995). Furthermore, it was reported that β-sitosterol helps to lower the increased levels of prostaglandins in BPH patients, while the pentacyclic triterpenoids block enzymatic activity, and in so doing, inhibit swelling or inflammation in the prostate (Bauer and Bach, 1986; Carbin et al., 1990; Holm and Meyhoff, 1997; Wasson and Watts, 1998; Quilez et al., 2003). Oral administration of *P. africana* extracts to rats reduced inflammation due to the release of histamine, as a result of lowering vascular permeability (Marcoli et al., 1986). Friedelin, present in *P. africana*, was proven to possess anti-inflammatory properties, since the compound inhibited acetic acid-induced vascular permeability in mice by as much as 54.5% in the carrageenan-induced hind paw oedema model (Catalano et al., 1984; Antonisamy et al., 2011). Using the same model, Mutuma et al. (2020) recently confirmed these findings after evaluating the anti-inflammatory activity of a dichloromethane stem-bark extract, administered to mice at 50, 100 or 150 mg/kg/bw. Ursolic acid has been reported to have anti-inflammatory activity in RAW264.7 mouse macrophages by downregulating the expression of pro-inflammatory mediators, induced by lipopolysaccharide (LPS) (Nataraju et al., 2007; Amico et al., 2009).

Ethanolic and aqueous extracts of *P. africana* were tested for anti-inflammatory activity (250 μg/mL) using cyclo-oxygenase-1 (COX-1)

and -2 (COX-2) assays. The ethanolic and aqueous extracts inhibited prostaglandin biosynthesis catalysed by COX-1, by 98% and 72%, respectively. The aqueous extract was less active in inhibiting prostaglandin biosynthesis catalysed by COX-2, while the ethanolic extract was inactive (Steenkamp et al., 2006). Cristoni et al. (2000) reported that *P. africana* extract inhibited the production of chemotactic leukotrienes, induced through 5-lipoxygenase (5-LOX) in human polymorphonuclear cells, which had been stimulated with the calcium ionophore A23187. Further studies (Papaioannou et al., 2010; Roell and Baniahmad, 2011) also investigated the effects of a non-polar bark extract of *Pygeum* on 5-LOX metabolites including leukotriene B4 (LTB4) at 3 ng/mL, 5-hydroxyeicosatetraenoic acid (5-HETE) at 1 ng/mL, 20-carboxy-LTB4 at 3 ng/mL and 20-hydroxy-LTB4 at 10 ng/mL in human polymorphonuclear cells that were stimulated as before.

The anti-inflammatory activities of β-sitosterol and ursolic acid on the prostate gland may confer anti-prostate cancer activity (Nyamai et al., 2016). Recently, methanolic extracts of *P. africana* (150 μg/mL) and isolated compounds (chlorogenic acid, catechin, naringenin, and β-sitosterol (100 μM each)) were tested for inhibition on NO production in RAW264.7 cells stimulated with LPS, as well as inhibition of IL-6 secretion level in macrophages. When compared to the positive control, dexamethasone, all sample extracts significantly inhibited NO production after LPS stimulation. IL-6 secretion was dramatically inhibited by methanolic extracts of *P. africana* (Komakech et al., 2022b). It is evident that *P. africana* extracts exhibit an anti-inflammatory effect and probably by several biochemical mechanisms.

7.2. Antimicrobial activity

The increasing resistance of microbial pathogens to widely used antibiotics and antiviral agents has encouraged researchers to investigate plants as sources of metabolites with anti-infective properties. Mwitari et al. (2013) reported that the methanolic stem-bark extract of *P. africana* was very active, with a minimum inhibitory concentration (MIC) of 0.78 mg/mL, against *Staphylococcus aureus*. However, the extract displayed poor activity towards methicillin-resistant *S. aureus* (MRSA), as reflected by the MIC of 3.125 mg/mL. In contrast, the ethyl acetate extract exhibited no activity towards both strains (MICs 12.5 and 25 mg/mL, respectively). An investigation conducted by Bii et al. (2010) in which they tested methanol and hexane stem-bark extracts of *P. africana* against the fungal or bacterial pathogens (*Pseudomonas aeruginosa* ATCC 27852, *S. aureus* ATCC 25923, *Streptococcus pneumoniae, Cryptococcus neoformans* ATCC 66031, MRSA, *Candida albicans* ATCC 90028, *Trichophyton mentagrophyte,* and *Microsporum gypseum*), indicated strong activity only against *S. aureus* (MIC 0.073 mg/mL), *T. mentagrophyte* (MIC 0.039 mg/mL) and MRSA (MIC 0.156 mg/mL). The methanol and hexane extracts were inactive towards the yeasts, *C. albicans* and *C. neoformans*. Various solvent extracts (chloroform, petroleum ether, methanol, and acetone) of the bark were tested against *Escherichia coli, S. aureus, Proteus mirabilis, Citrobacter freundii, Enterobacter cloacae, Enterobacter* spp., *Klebsiella pneumoniae, Enterobacter aerogenes, Citrobacter koseri* and *Staphylococcus pyogenes* (Gashe and Zeleke, 2017). The acetone extract of *P. africana* was the most effective with a MIC of 0.65 mg/mL against *S. pyogenes* and *C. freundii,* while the methanol extract displayed the best activity towards most of the strains. Ngule et al. (2014) assessed the *in vitro* antibacterial activity of bark extracts, prepared using aqueous methanol, against several bacterial pathogens using the disc diffusion assay. *Salmonella typhi* had the largest zone of inhibition (ZI = 17.33 ± 0.882 mm) as compared to penicillin used as a positive control (ZI = 27.67 ± 1.202 mm), followed by *P. vulgaris* (ZI = 16.67 ± 0.333 mm) and *Serratia marcescens* (ZI = 16.67 ± 0.333 mm), while *E. coli* and *Bacillus cereus* were the least susceptible. Gangoué-Piéboji et al., 2007) evaluated the anti-β-lactamase activity of the methanol extract of *P. africana* bark against various classes of β-lactamases (TEM-1, IMP-1, OXA-10 and P99), as β-lactamase is an enzyme which is responsible for resistance to β-lactam antibiotics like penicillins, monobactams, cephalosporins and carbapenems (Bialvaei et al., 2015). The reports have shown the percentage inhibition values of 73.9%, 85.0%, 48.6%, and 75.2%, respectively. The search for β-lactamase inhibitors from herbal medicines, which preserves β-lactam antibiotics from the effect of the β-lactamase, has given scientists a novel tactic to control resistant microbes (Bush, 1988). Dey et al. (2017) investigated the antimicrobial effect of an ethanolic extract of *P. africana* stem-bark on *Shigella* species (*S. flexneri* – two strains, *S. dysenteriae* and *S. boydii*). The solvent, dimethyl sulfoxide (DMSO) was used as negative control and chloramphenicol as positive control. The results reflected antibacterial activity towards *S. boydii* (ZI = 10 mm) as compared to chloramphenicol (ZI = 33 mm), followed by the *S. flexneri 4a*, *S. flexneri 2a*, *S. dysenteriae* and *S. boydii* (ZI = 9 mm) and a MIC of 2.625 mg/mL for all the tested strains, reflecting poor activity. Recently, Deresa et al. (2022) evaluated the antibacterial properties of the methanol stem-bark extracts and compounds isolated from *P. africana* against *E. coli* (ATCC25922), *S. aureus* (ATCC25923), *Shigella flexineri* (ATCC29903), *S. typhimurium* (ATCC13311) and *P. aeruginosa* (ATCC27853) using the disc diffusion assay. The results indicated considerable activity of the crude extract against both Gram-positive and Gram-negative bacterial strains. The largest ZI was recorded for cultures of *P. aeruginosa* (ZI = 21.03 ± 0.05 mm), greater than gentamicin (ZI = 14.06 ± 0.09 mm), followed by *S. flexineri* (ZI = 14.23 ± 0.21 mm) and *S. aureus* (ZI = 11.10 ± 0.08 mm). Conversely, the isolated compounds showed moderate activity against all the test strains. A study conducted by Ssekatawa et al. (2021) in which they tested the efficacy of synthesis of silver nanoparticles (AgNPs) using *P. africana* and *Camellia sinensis* water extracts against carbapenem-resistant bacteria *E. coli* and *K. pneumoniae*. *Prunus africana* extract biosynthesised AgNPs exhibited maximum growth inhibitory zones of 20 mm against carbapenem-resistant bacteria, with minimum inhibitory concentration and minimum bactericidal concentrations of 125 and 250 μg/mL, respectively.

Ssekatawa et al. (2022) explored the efficacy of aqueous extracts of *P. africana* bark and *Camellia sinensis* (black tea) against *S. aureus*, *K. pneumoniae* and *E. coli*. The results showed that *P. africana* bark aqueous extract yielded the largest inhibition zone (ZI = 30 mm) against *S. aureus*, followed by *K. pneumoniae* (ZI = 27 mm) and *E. coli* (ZI = 26 mm) with MIC of 30 μg/mL against *S. aureus* and 125 μg/mL against *K. pneumoniae* and *E. coli*.

Most of the studies done were based on the disc diffusion assay, which is not a good assay for determining antimicrobial activity since the polarities of the compounds determine how well they diffuse into the polar agar medium and subsequently affect the size of the inhibition zone. In contrast, agar dilution and broth microdilution methods can overcome some of the limitations of the disc diffusion method. Not only are they more convenient for routine antimicrobial susceptibility testing of bacteria in clinical laboratories, but they are also capable of drawing quantitative conclusions by determining the MIC values for antimicrobials, as opposed to data generated by the disc diffusion method (Kim et al., 2007).

7.3. Anti-oxidant activity

The consumption of anti-oxidants derived from natural sources has increased, due to consumer awareness of the potential preventative effects of anti-oxidants against diseases such as arthritis and cancer (Sharifi-Rad et al., 2020). The production of reactive oxygen species (ROS) and nitrogen species through both endogenous and exogenous processes, as well as the use of anti-oxidants as therapeutic interventions, is discussed in a review by Liguori et al. (2018). Various studies have shown that several secondary metabolites produced by *P. africana* have excellent anti-oxidant properties.

A chloroform extract of *P. africana* bark was fractionated using solvent-solvent partitioning, followed by column chromatography, for evaluation of inhibitory activity against Fe^{3+}-induced stimulation of lipid peroxidation in microsomal preparations of rabbit livers. The

fractions and extract contained high concentrations of myristic acid (20 μg/mL), which strongly inhibited lipid peroxidation in the microsomal preparations by 97%, comparable to α-tocopherol (Hass et al., 1999). Crude water and ethanolic extracts (4 mg/mL) of bark were investigated for their effect on hydroxyl scavenging activity. The water extract was highly active (80% scavenging activity) compared to the ethanol extract (less than 50% activity). The control, Vitamin C, showed scavenging activity of 76% and 96% at concentrations of 80 mg/L and 160 mg/L, respectively (Steenkamp et al., 2006). Ethyl acetate and methanolic extracts of the bark, in which the presence of phenolic compounds and flavonoids was confirmed by Fourier Transform infrared spectroscopy (FT-IR), displayed anti-oxidant activity when tested in the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay (Madivoli et al., 2018). Ssekatawa et al. (2022) evaluated the anti-oxidant activity of *P. africana* bark extract, *Camellia sinensis* extract and the green synthesised CuONPs using DPPH assay. The results showed that *P. africana* exerted substantial anti-oxidant activity with a free radical scavenging activity of 70.2% compared to ascorbic acid used as a positive control (70.8%) at a concentration of 300 μg/mL.

The investigation of natural anti-oxidant compounds from herbal medicines would continue to play a great role in the scientific world. This is due to the increasing understanding of the role of oxidative stress in damaging cell structures, because of the over-production of free radicals and reactive oxygen species (ROS) in human systems (Stanković et al., 2016). Most plant compounds characterised by anti-oxidant activity are polyphenols. Anti-oxidant activity cannot be directly related to any specific disease condition. However, various animal models can be used to evaluate the role of anti-oxidants in inhibiting conditions in which oxidative stress plays a role such as inflammation, cancer and diabetes.

7.4. Antiviral activity

The nature and morphology of viral pathogens are inherently complex, so specific treatments for many viral infections are lacking. To function, most viruses are reliant on the cellular metabolic processes, since their intrinsic enzyme systems and building blocks, which are targeted during drug development, are limited. In many cases, ethnopharmacological evidence serves as a guide for the selection of plants for the isolation of antiviral compounds (Ogbole et al., 2018). Ideally, the plant extract must inhibit the virus completely, without being toxic towards the host cell (Colegate et al., 1993). Rukunga et al. (2002) screened 22 medicinal plants (including *P. africana*), identified as popular remedies to treat patients infected with human immunodeficiency virus type 1 (HIV–1). They reported that eight extracts exhibited ≥50% reverse transcriptase inhibition activity at various concentrations, among which *P. africana* bark was included. Another study conducted by Tolo et al. (2006) demonstrated the potent antiviral effects of an aqueous extract of the stem-bark of *P. africana* against herpes simplex virus (HSV) and human cytomegalovirus (HCMV). The effective concentration inhibiting plaque formation by 50% (EC_{50}) was recorded as 80 μg/mL (Tolo et al., 2007). In addition, a safe therapeutic index was indicated by evaluating the cell viability of stem-bark tested. The concentration of the stem-bark reduced cell viability by 50% (CC_{50}), using the Trypan Blue exclusion test. A study was carried out on CareVid, a multi-herbal product made up of 14 medicinal plants, including *P. africana*, which plants grow in the southwestern parts of Kenya and is used as an immune booster and health tonic for the treatment and management of HIV-positive patients. The objective of this study was to screen the different CareVid extracts of using different extractant solvents for *in vitro* and *in* silico activity against the HIV-1 reverse transcriptase enzyme and determine the major chemical constituents them using HPLC-MS. The results showed that MeOH and 80% EtOH extracts inhibited HIV-1 reverse transcriptase *in vitro*, with an EC_{50} of 7 μg/mL. Among the major components identified, ellagic acid and procyanidin B inhibited the HIV-1 reverse transcription process at 15 and 3.2 μg/mL, respectively (Rotich et al., 2021). In 2022, Rotich conducted a survey review on the same CareVid. Through the review, it has been found that polyphenolic compounds present in the stem-bark extracts of *P. africana* are thought to be responsible for HIV-1 reverse transcriptase enzyme inhibition activity at inhibitory concentrations of 50 and 100 μg/mL (Rukunga et al., 2002).

7.5. Antimutagenic activity

In vivo and *in vitro* mutagenicity studies indicated a total absence of mutagenic and clastogenic potential of stem-bark *P. africana* extract (European Scientific Cooperative on Phytotherapy, 2009). Aqueous methanol (90%) and dichloromethane extracts of *P. africana* were tested for mutagenic activity in micronucleus and microsome/Salmonella assays. *Prunus africana* extracts did not alter the effect of the mutagen, 4-nitroquinoline-oxide (4NQO), and no mutagenicity was observed in the *S. typhimurium* TA98 strain (Elgorashi et al., 2003; Verschaeve et al., 2004). Extracts of *P. africana* significantly reduced the effect of the mutagen, mitomycin C (MMC), in the *in vitro* micronucleus test in human lymphocytes, and there was no indication of genotoxicity (Verschaeve et al., 2004).

7.6. Antiproliferative and apoptotic activities

Cell proliferation is an increase in cell numbers as a result of cell growth and division. Cells within a tissue normally exert an inhibitory effect on each other's growth. It has been proposed that bark extracts of *P. africana* have a beneficial effect on prostate cancer patients, since they reduce urologic symptoms due to their apoptotic and antiproliferative effects on the prostate (Nyamai et al., 2015). An ethanolic bark extract, tested *in vitro* against two cancer cell lines (PC-3 and LNCaP cells) caused growth inhibition of both induced cell death and caused alteration of the kinetics of the cells. Both ERα and PKC-α proteins were downregulated and increased binding ability to both mouse uterine oestrogen receptors and LNCaP human androgen receptors (Shenouda et al., 2007). In the TRAMP mouse model, the ethanolic bark extract at a concentration of 0.128 mg/kg, resulted in a significant and marked reduction of well-differentiated carcinoma tumour incidence (35%) compared to mice fed a casein diet (62.5%). This study showed that *P. africana* at 2.5 μL/mL was responsible for an accumulation of the cells in the S-phase of the cell cycle, for both PC-3 and LNCaP cells (Shenouda et al., 2007).

The effect of stem-bark extract on the proliferation of cultured human prostatic fibroblasts and myofibroblasts was investigated by Boulbès et al. (2006). 5-Bromo-2′-deoxy-uridine (BrdU) incorporation assays were employed for cell proliferation measurements, and cytotoxicity was determined using luminescent quantification of adenylate kinase activity. The results from the incorporation tests demonstrated that the proliferation of the cultured human stromal cells, stimulated by basic fibroblast growth factor, by both foetal calf serum and epidermal growth factor, was inhibited by *P. africana* extracts (5–100 μg/mL) in a dose-dependent manner. The extract did not cause acute cytotoxicity after 24 h of culture, except at a concentration of 100 μg/mL. In a similar manner, but to a lesser extent, the extract inhibited the proliferation of Madin–Darby canine kidney epithelial cells, dose-dependently and no acute toxicity was observed in the cell line.

Previous reports have shown that extracts of *P. africana* used in the treatment of BPH, inhibited the proliferation of prostate stromal cells from BPH tissues (Quiles et al., 2010). To establish the mode of action, an investigation of the apoptotic and proliferative responses induced by *P. africana* in both non-BPH and BPH prostate stromal cells, focusing on the specific reaction displayed by stromal cell subsets was done. Primary prostate stromal cells obtained from patients not undergoing BPH cystectomy, as well as from patients with lower urinary tract symptoms or BPH and undergoing open prostatectomy, were exposed to bark extracts of *P. africana*. On the other hand, apoptosis, transforming growth factor B1 (TGFB1), fibroblast growth factor 2 (FGF2), vimentin, α smooth

muscle actin (αSMA), and smoothelin expression were examined after bark extract treatment. Cell immunophenotype and proliferation were tested after incubating cells with bark extracts plus either FGF2, TGFB1, vascular endothelial growth factor (VEGF), dihydrotestosterone (DHT) or 17β-estradiol (E2).

It was found that apoptosis and antiproliferative activity induced by *P. africana* were higher in BPH cells compared to non-BPH cells. The bark extracts downregulated TGFB1 expression and FGF2 increased cell sensitivity to *P. africana*. In contrast, incubation with mitogenic factors, such as DHT, VEGF, and E2, decreased cell sensitivity to *P. africana*. Both E2 and TGFB1 stopped the antiproliferative activity of *P. africana*. *Prunus africana (*indicated as *Pygeum africanum*) extract (Tadenan®) is formulated for the treatment of micturition disorders associated with BPH. Its effect on the proliferation of rat prostatic stromal cells, stimulated by different growth factors, was investigated by Yablonsky et al. (1997). Tadenan® inhibited both stimulated and basal growth, with half-maximal inhibitory concentration (IC_{50}) values of 7.7 μg/mL, 4.5 μg/mL, and 12.6 μg/mL for IGF-I, EGF, and bFGF, respectively, in comparison to 14.4 μg/mL for untreated cells. The results indicated that *P. africana* acts as a strong inhibitor of the proliferation of rat prostatic fibroblasts, in response to the defined growth factors EGF, bFGF and IGF-I. It was concluded that the therapeutic effect of the plant can wholly, or partially, be attributed to the inhibition of growth factors responsible for prostatic overgrowth in humans (Yablonsky et al., 1997).

The pathogenesis of BPH is associated with growth factors, in particular, basic fibroblast growth factor (b-FGF), which is present at higher concentrations in BPH tissues than in normal prostatic tissues. It has been established that b-FGF, EGF (epidermal growth factor) and dihydrotestosterone DHT enhance the growth of fibroblasts in the adult prostate (Bombardelli and Morazzoni, 1997). A non-polar extract of *P. africana* bark significantly inhibited the proliferation of 3T3 mouse fibroblasts stimulated by b-FGF and EGF at a concentration of 1 μg/mL) (European Scientific Cooperative on Phytotherapy, 2009).

A study was conducted to evaluate the mode of action and the safety of dichloromethane stem-bark extracts of *P. africana* using the cell counting Kit 8 cell proliferation assay (Mwitari et al., 2013). The levels of interleukin 7 (IL 7) cytokine were monitored *in vitro,* using IEC-6 cells and reverse transcription polymerase chain reaction (RT-PCR) techniques. The plant extract, at a concentration of 50 μg/mL, downregulated the expression of IL 7 mRNA. The mode of action was found to be related to gene silencing, cytotoxicity and immunopotentiation. *Prunus africana* yielded an IC_{50} cytotoxicity value greater than 100 μg/mL when tested in IEC-6 cells, which is normally considered quite safe.

Nabende et al. (2015) studied the antiproliferative activity of both water and methanol extracts of *Warburgia stuhlmannii, P. africana,* and *Maytenus senegalensis* in colon cancer (CT26.WT-ATCC® CRL-2638™) and breast cancer (4T1 ATCC® CRL-2539™) cell lines and determined the toxicity of each extract based on responses in Swiss albino mice and towards Vero cells. The results demonstrated that the methanolic leaf extract of *P. africana* is safe and effective with an average IC_{50} of 164.64 ± 4.14 μg/mL in the breast cancer cell lines and 21.33 ± 0.5 μg/mL in the colon cancer cell lines. The safety of the methanol extract of *P. africana* in the murine model and its antiproliferative activity in both colon and breast cancer cells were confirmed, with no indication of toxicity to Vero cells (Nabende et al., 2015).

The effect of acetone, dichloromethane, ethanol and methanol leaf, bark and root extracts of *P. africana* on the proliferation of prostate cancer C4-2 cells was investigated *in vitro*, using different concentrations (Asuzu et al., 2021). Growth inhibition of C4-2 cells by both methanol bark and root extracts was reported, with complete lysis of all cells observed above 0.05 mg/mL. The methanol extract of the bark showed the strongest effect. Although the leaf extracts were significantly less cytotoxic compared to other plant parts, a distinct grouping of cells and proliferation was evident, compared to the control (Asuzu et al., 2021). Komakech et al. (2022a) recently evaluated the *in vitro* cytotoxic effects of micropropagated root on PC-3 prostate cancer cells, as a possible alternative to the *P. africana* stem-bark extract treatment used traditionally for cancer. The efficacy of the six-month-old micropropagated root, extracted with ethanol, was found to be lower (IC_{50} value 82.40 μg/mL) than that of the stem-bark extracts endangered wild *P. africana* (IC_{50} 52.30 μg/mL). Nevertheless, these findings demonstrated the antiprostatic cancer potential of micropropagated *P. africana* and lay the basis for further studies using this technique, as an alternative to harvesting stem-bark. Micropropagation also has important implications for preparing remedies for BPH treatment. The presence of ferulic acid esters and their derivatives has also been linked to the antitumor and hypocholesterolemic activities of *P. africana* bark extract on the prostate (Nyamai et al., 2016). According to Lui et al. (2014), oleanolic acid has antitumor activity by interfering with a metabolic pathway in prostate cancer cells by activating the enzyme 5′-AMP-activated protein kinase (AMPK).

7.7. Anti-asthmatic activity

Asthma is a serious respiratory condition stemming from constriction of the airways, which become inflamed and covered with a lining of excessive mucus. Chronic and recurrent airflow obstruction may set in, causing frequent wheezing and/or coughing, lack of breath, tightness in the chest area and sputum production (GINA, 2018). Karani et al. (2013) induced asthma in BALB/c mice to investigate the safety and efficacy of stem-bark extracts of *P. africana* and *W. ugandensis* as treatments for asthma. Efficacy was determined by an assay of ovalbumin specific immunoglobulin E (IgE) antibodies in heart blood serum and by quantification of eosinophil proportion in bronchoalveolar lavage fluid (BALF). The *P. africana* extracts administered at 500 mg/kg reduced IgE at ($OD_{450\ mn} = 0.100 \pm 0.0001$ and BALF eosinophil levels at 2.80 ± 0.20% as compared to the reference drug ($OD_{450\ mn} = 0.100 \pm 0.00012$ and 3.60 ± 0.245%), respectively, which were significantly different from those of the positive controls ($p < 0.05$). Although it could be deduced that *P. africana* stem-bark extracts exhibited anti-asthmatic activity, the mechanism of action was not elucidated and could be the topic of future studies in this regard.

7.8. Anti-androgenic activity

A study by Papaioannou et al. (2009) revealed the important role of androgens to the development of BPH and prostate cancer. The most abundant androgens in adult males are testosterone, present mainly in the blood circulation, and dihydrotestosterone (DHT), found mainly in tissue and is also the most potent. The androgenic effects in the prostate are exerted *via* interaction with the androgen receptor (AR) protein. Androgen antagonists that block the AR-mediated gene transactivation can therefore be used as anti-androgenic treatments. Atraric acid (AA), isolated from bark material of *P. africana,* was found to have anti-androgenic effects, by impeding transactivation that is mediated by the ligand-activated human AR. However, the androgen antagonistic activity was found to be specific to the AR protein, since the structurally similar glucocorticoid as steroids or progesterone receptors were not inhibited (Papaioannou et al., 2009). The anti-androgenic activity of a dichloromethane stem-bark extract was determined by Schleich et al. (2006a) at 300 μg/mL and 600 μg/mL. Together with extracts of other ethnobotanical species, using an AR responsive reporter gene assay, fractions F7 and F8 prepared from the dichloromethane extract of *P. africana* were substantially more effective than the others at 30 μg/mL and 60 μg/mL, respectively. N-Butylbenzenesulfonamide (NBBS) was isolated through bioactivity-guided fractionation F8 of this extract. The same research group (Schleich et al., 2006b) also isolated the anti-androgenic compound, atraric acid, from the dichloromethane stem-bark extract through bioactivity-guided fractionation. Its activity was established using an androgen receptor-responsive reporter gene assay. The isolated atraric acid revealed similar inhibition of AR

function at a concentration of 1.0 μM as compared to that of the commercially available atraric acid. Roell and Baniahmad (2011) investigated the anti-androgenic activity of both isolated compounds from the dichloromethane extract of *P. africana*. Both atraric acid and *N*-butylbenzene-sulfonamide exhibited inhibitory activity of human AR at a concentration of 1.0 μM, and complete inactivation of human AR at 10 μM and 100 μM. An IC_{50} of 10 μM was determined for NBBS for the inhibition of hormone-activated AR. Both compounds are the first known natural, complete and specific AR antagonists.

7.9. Pre-clinical studies

Researchers have found that the contractile dysfunction observed in animals, in which partial bladder outlet obstruction has been induced, is caused by focal ischemia/reperfusion (I/R). Tadenan® (*P. africana*) was administered at a clinically relevant dose as a pre-treatment to rabbits (Levin et al., 2005) to establish the protective effects of the drug in the bladder against injury induced by bilateral ischemia followed by reperfusion. New Zealand white rabbits were divided into two groups; the first was pre-treated for three weeks with Tadenan (3.0 mg/kg bw/day) *via* oral gavage, while the second (control) group was treated with peanut oil. The results indicated that pre-treatment with 3.0 mg/kg/bw/day Tadenan® (as opposed to an earlier study in which 100 mg/kg/bw/day were used) safeguards the bladder from the contractile dysfunctions associated with bilateral ischemia followed by reperfusion. The authors concluded that their study provided evidence that Tadenan® protects the bladder from ischemia.

7.10. Clinical studies

Several open and double-blind placebo-controlled clinical studies have been conducted to evaluate the efficacy of *P. africana* to prevent and treat symptoms associated with mild and moderate BPH (Barlet et al., 1990; Bombardelli and Morazzoni, 1997; Csikós et al., 2021). A critical analysis was done of 18 double-blind, placebo-controlled studies that assessed the ability of an orally administered lipophilic stem-bark extract to reduce the symptoms of 717 male patients with mild to moderate BPH. The individual studies involved as few as 14 patients, to as many as 255, with dosages ranging from 75 to 200 mg, taken daily for a period of 6 weeks to 3 months. Eight of the studies recorded the maximum urinary flow of the patients and 10 studies measured daytime and night-time polyuria (Barth, 1981; Dufour et al., 1984). The efficacy of a trunk bark extract to treat micturitional disorders related to BPH was investigated in a multicentre double-blind placebo-controlled trial *versus* a controlled trial. A dosage of 50 mg of the extract (one capsule) or placebo was administered bi-daily for 60 days. A total of 263 patients were included at eight sites in Germany, France and Austria. A marked improvement of 66% in micturition (as measured by residual urine, uroflowmetry and diurnal and nocturnal pollakiuria) was reported for the treatment group, as compared with an improvement of 31% in the placebo group (Barlet et al., 1990). One study made use of a combination of the stem-bark extract and medroxyprogesterone acetate as a standard of treatment. A significant increase in urinary flow, following treatment with the extract, as compared to placebo, was reported in seven trials (Barth, 1981; Dufour et al., 1984). An earlier study, involving a relatively small number of patients, had reported that there was no significant difference between the outcomes of Tadenan®--treated and placebo-treated patients (Donkervoort et al., 1977).

Histological examination of prostate tissue biopsies from patients diagnosed with BPH and given 75 mg of a lipophilic stem-bark extract daily for 1–3 months, indicated higher prostate secretion levels, but no reduction in prostate size (Doremieux et al., 1973). In patients with abnormally low levels of total protein secretion, the treatment re-established the normal levels of secretion from the prostate and restored the activity of prostate acid phosphatase (Luchetta et al., 1984). Wilt and Ishani (1998) found that the efficacy of *P. africana* was only moderately more effective than placebo in the treatment of BPH, as determined by urologic and flow measures, but that the herbal drug had fewer side effects compared to standard BPH drugs. Men using *P. africana* were more than twice as likely to report an improvement in overall symptoms (RR = 2.1, 95% CI = 1.4 to 3.1). Nocturia was 19% lower, residual urine volume decreased by 24% and peak urine flow increased by 23% in treated subjects.

Several uncontrolled clinical trials were carried out in the 1970s; fourteen of these trials indicated an improvement in outcomes following oral treatment with a chloroform extract of stem-bark in 461 men, with stage I or II BPH (Lhez and Leguevague, 1970; Robineau and Pelissier, 1976). In ten of the studies, a 100 mg dose was given to 281 patients for 21 days to three months, and in four studies, a total of 180 patients received 75 mg extract daily for 21 days to three months. In all but three studies, the global outcome was assessed as either excellent, very good, good, or improved, in over 50% of the patients. Data from 19 other clinical trials without controls, involving 18 to 59 males per study and a total of 849 male patients with BPH, revealed a significant improvement in their symptoms after treatment with a lipophilic stem-bark extract (Andro and Riffaud, 1995). Patients were administered daily with extract: either 200 mg extract (148 patients), 150 mg (42 patients), 100 mg (523 patients), 75–100 mg (20 patients) or 75 mg (116 patients), for a period of 20–160 days. Improvements in daytime polyuria, nocturia, mean maximum urinary flow rate and postvoid residual volume were demonstrated in more than half of the patients in the various studies. Symptoms such as urgency and hesitancy of micturition and dysuria were also improved.

A large open-label, non-placebo-controlled study evaluated improvements in urodynamic parameters brought about by the treatment of 500 men diagnosed with BPH with a lipophilic extract of the bark for a period of more than five years. The extract was taken daily, but no doses were provided. More than 68% of patients reported improvements in dysuria, daytime polyuria and nocturia. Increased urinary volume and flow rate were reported in over 61% of participants. The most notable improvements were observed in moderately affected patients, those who did not have a prominent median lobe of the prostate, and those with a below 100 mL baseline postvoid residual volume (Andro and Riffaud, 1995). Improvement in prostate secretion was only reported in the absence of prostate infection (Clavert et al., 1986).

A multicentre non-controlled study assessed the safety and efficacy of a stem-bark extract (50 mg), taken bi-daily for 2 months, by 85 men with symptoms of BPH (stage of B moderately PH not specified) were evaluated (Breza et al., 1998). The International Prostate Symptom Score (IPSS) and the Quality-of-Life score (QL) were used as subjective assessments, and urine flow was measured to ensure an objective evaluation. After treatment, the IPSS and QL improved significantly ($p < 0.001$) by 40% and 31%, respectively. A significant ($p < 0.001$) reduction of 32% in nocturia was reported. Hirsh et al. (2020) evaluated the self-assessed benefits of a prostate health dietary supplement containing β-sitosterol (*P. africana*) on thirty healthy male subjects with mild LUTS, who took one daily capsule of the product for 60 days and complete the International Prostate Symptoms Score (IPSS) questionnaire at Day 1 (baseline), Day 30 and Day 60. The results showed that IPSS decreased by 16.3% from baseline at day 60. Although the reduction in IPSS did not reach statistical significance at Day 30, it was primarily driven by a 30.7% decrease ($p < 0.05$) in the nocturia sub-score compared with baseline. While 37% of subjects reported waking up 2–3 times per night to void at baseline, none did so after taking the study product for 60 days. Throughout the study, compliance was extremely high. There were no adverse events related to the study product.

Recently, Cambronero et al. (2022) evaluated the efficacy and tolerability of treatment with *P. africana* (Tebetane®) in 115 patients with LUTS/BPH in routine clinical practice for 6 months by assessing the Quality of Life (QoL) based on changes in the scores of item 8 of the International Prostate Symptom Score (IPSS) and observing improvement of urinary symptoms, urinary flow, satisfaction and compliance

with treatment as well as tolerability. The results revealed that, after 6 months of treatment with *P. africanum*, the percentage of patients with significant impairment of QoL was 22.6% as compared with 45.2% at the start of treatment (P < 0,-001). The overall IPSS score decreased by -4, -5 points, with 69 patients (60%) showing clinically significant improvement (reduction of ≥4 points). Leisegang et al. (2022) reviewed the published evidence investigating the use of herbal medicines (including *P. africana*) as a treatment for BPH in clinical trials based on PRISMA guidelines. The literature search revealed that, in a total of 1561 articles retrieved, only 28 articles were included. *Prunus africana* intervened at 14% either in isolation or in combination with other herbs/components, as an improvement in symptoms associated with BPH (IPSS/AUASI, Qmax, PSA, QoL scores, PRV and PV).

7.11. Other activities

Prunus africana is one of the herbal medicines available in local markets to treat diabetic conditions (Maina et al., 2014). Indeed, *P. africana* extract was found to be capable of inhibiting the dipeptidyl peptidase-4 (DPP-4) enzyme, which is known to be essential for the inactivation of glucagon-like peptide (GLP-1) resulting in increased insulin production in the body; an important factor in the management of Type 2 diabetes mellitus due to the controlled body glucose level (Singh et al., 2015). As a result, the ability of *P. africana* to increase GLP-1 activity supports its use in traditional medicine for the management of diabetes mellitus (Komakech and Kang, 2019). When adult Wistar male rats were fed orally daily with 100 mg/kg of *P. africana* in peanut oil for 4 weeks after diabetes induction, the extract completely suppressed oxidative stress in diabetic bladders and slowed the process of diabetic cystopathy (Wang et al., 2010). Furthermore, in alloxan-induced diabetic rats, *P. africana* aqueous and ethanolic extracts demonstrated significant hypoglycemic activity (Maina et al., 2014).

Komakech et al. (2022b) conducted the macrophage-dependent *in vitro* anti-osteoporosis activity of *P. africana* stem-bark extracts. In the 96-well plates, mouse bone marrow macrophages (BMM) cells were treated for 24 h with *P. africana* methanolic stem-bark extracts at concentrations of 0, 6.25, 12.5, 25, and 50 μg/mL, as well as with chlorogenic acid, catechin, naringenin, and β-sitosterol. The activity of tartrate-resistant acid phosphatase (TRAP) in osteoclasts was measured. At all concentrations, *P. africana* methanolic extract significantly inhibited RANKL-induced TRAP activity.

Ndegwa et al. (2022) recently investigated the antischistosomal properties of medicinal plants (including *P. africana*) commonly used by indigenes in Kenya for the treatment of various ailments such as malaria, pneumonia, and diarrhoea. Extracts were tested against *Schistosoma mansoni* newly transformed schistosomula (NTS)and adult worms. After 24 h of exposure, acetone extracts of *P. africana* (100 μg/mL) with steroids, anthraquinones, and glycosides as major compounds reduced NTS viability by 96.4%. The summary of the biological activities of specific compounds or extracts of *P. africana* is presented in Table 3..

8. Toxicity

The use of a medicinal plant, without full scientific evaluation of its toxicity, poses a serious risk to health, and in some cases, has dire consequences (Fall et al., 2011). The toxicity of a plant is influenced by factors including the concentrations of potentially toxic secondary metabolites, the quantity of the drug consumed, the time of exposure, the body chemistry of the patient, as well as genetic differences within the species and environmental factors that determine the chemical profile of the plant (Mounanga et al., 2015). Several studies have been conducted to investigate the cytotoxicity of different species of the genus *Prunus*. Although various plant parts of *P. africana* have been reported to be poisonous, the available literature indicates that the extract is well tolerated in a variety of animal models (rats, mice, guinea pigs and dogs) and in human subjects. Mild gastrointestinal symptoms were only reported in a few cases after use.

Bombardelli and Morazzoni (1997) reported that after intragastric administration of a single, high dose of a non-polar stem-bark extract of *P. africana* (1–8 g/kg in rats and 1–6 g/kg in mice), no side effects or deaths were reported. In addition, a chronic toxicity study involving intragastric administration of 600 and 60 mg/kg/bw, daily, for 11 months did not reveal adverse effects. The *in vitro* micronucleus test in human peripheral lymphocytes was used to monitor the genotoxic, cytotoxic and antimitotic activities of five secondary metabolites, isolated from *P. africana* and *Bupleurum fruticosum* (Scarpato et al., 1998). No increases in the frequency of nuclei were detected for any of the compounds at the concentrations tested.

Gathumbi et al. (2002) reported an increase in the body weight of Sprague Dawley male rats treated with daily doses of 10, 100 or 1000 mg/kg of chloroform stem-bark extract for eight weeks and suggested that the extract did not cause adverse side effects. The extract did not show clinical signs or changes in pathology in Sprague Dawley male rats, aged 8–10 weeks, at daily oral doses of up to 1000 mg/kg for 8 weeks (Gathumbi et al., 2002). However, a dose of 3.3 g/kg/bw was accompanied by the development of restlessness, rapid and deep breathing with terminal gasping, and involuntary muscle contractions that were characterised by the champing of the jaws and repeated jerking of the head.

Karani et al. (2013) evaluated the cytotoxicity of aqueous stem-bark extracts in Vero E6 cells using the 3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay and determined its acute toxicity in BALB/c mice. The results showed that there were signs of toxicity recorded with 20%, 60%, and 100% mortality within 24 h for mice that received *P. africana* extracts at 1581.64, 2812.15, and 5000 mg/kg/bw, respectively. These results indicate that aqueous stem-bark extracts are toxic at high concentrations. Nabende et al. (2015) demonstrated that a methanolic leaf extract of *P. africana* exhibited selective cytotoxic effects in mouse breast and colon cancer cells compared to monkey kidney (Vero) cells after drug administration with LD_{50} of >5000 ng/kg/bw.

Maiyo et al. (2016) evaluated three compounds isolated from the hexane, DCM and methanol sequential extraction of leaves and bark of *P. africana,* for potential cytotoxicity and induction of apoptosis in two human cancer cell lines (hepatocellular carcinoma (HepG2) and colorectal carcinoma (Caco-2)) and a non-cancer cell line (embryonic kidney (HEK293). *β*-Amyrin and *β*-sitosterol-3-*O*-glucoside exhibited strong cytotoxic activity towards the Caco-2 cell line with IC_{50} values of 81 μg/mL and 54 μg/mL, respectively. The HepG2 cell line was not susceptible, with IC_{50} values above 200 μg/mL recorded for the two compounds. Recently, Komakech et al. (2022b) conducted a hepatotoxicity assay of *P. africana* methanolic, ethanolic and water extracts (25, 50, 100,200 μg/mL) in zebrafish larvae from 90 to 120 hpf. At 50 and 100 μg/mL water extract concentrations, 30% and 10% of the zebrafish larvae survived at 120 hpf, respectively, and hepatocyte death was not observed. However, at a higher concentration of 200 μg/mL water extract, all larvae mortality was observed before 120 hpf. At 120 hpf, 50% of the zebrafish larvae survived at a concentration of 25 μg/mL ethanolic extract, and hepatocyte death was not observed. At higher concentrations of 50 and 100 μg/mL, however, 100% larvae mortality was observed at 120 hpf. Before the 120 hpf, larvae exposed to methanolic extracts at various concentrations of 25, 50, and 100 μg/mL died completely.

The biological and pharmacological properties of the isolated compounds are concisely presented in Table 3.

9. Quality control (QC) aspects

9.1. Introduction

In recent years, adulteration of herbal medicines with less costly or more abundant plant material has raised concerns (Ariffin et al., 2021).

Table 3
Biological activities reported for *Prunus africana* extracts and some isolated compounds.

Extract/compound	Assay	Organism/Cell line	Positive control(s)	Activity	Reference
Anti-inflammatory and analgesic activities					
Ethanol and aqueous extracts (dried bark)	COX-1and COX-2 inhibition assays	*In vitro*	Indomethacin (7.14 μg/mL (20 μM) and 71.4 μg/mL (200 μM) for the COX-1 and -2 assays, respectively)	Ethanol and aqueous extracts inhibited COX-1, by 98% and 72%, respectively. Aqueous extract was less active while the ethanolic extract was inactive in inhibiting COX-2	Steenkamp et al., (2006)
N-butylbenzene-sulfonamide (NBBS) ($C_{10}H_{15}NO_2S$: 213.29) (isolated from the bark dichloromethane extract)	Inhibition of androgen receptor (AR) transactivation	*In vitro*	Methyltrienolone ($3x10^{-10}$ μM)	NBBS inhibited transactivation of human AR and the growth of the human LNCaP PCa cells.	Papaioannou et al., (2010)
Antimicrobial activity					
Dichloromethane, ethyl acetate and methanol extracts (stem-bark)	Disc diffusion assay	*Staphylococcus aureus* (SA) *ATCC 25923,* methicillin-resistant *S. aureus* (MRSA)	Chloramphenicol (30 μg/mL) and fluconazole (25 μg/mL)	Methanol extract was active against both *S. aureus* and MRSA (MIC = 0.78 mg/mL and 3.125 mg/ml, respectively). Ethyl acetate extract was moderately active against *S. aureus* (MIC = 12.5 mg/mL) and MRSA (MIC = 25 mg/mL)	Mwitari et al., (2013)
Chloroform, petroleum ether, methanol, and acetone extracts (dried bark)	Disc diffusion assay	*Escherichia coli, S. aureus, Proteus mirabilis, Citrobacter freundii, Enterobacter cloacae, Enterobacter* spp., *Klebsiella pneumoniae, Enterobacter aerogenes, Citrobacter koseri* and *Staphylococcus pyogenes*	Ceftriaxone (30 μg/mL) and cefepime (30 μg/mL)	Acetone extract was the most active extract with MIC of 0.65 mg/mL against *S. pyogenes* and *C. freundii,* while the methanol extract displayed the best activity towards most of the strains.	Gashe and Zeleke, (2017)
Hexane and methanol extracts (stem-bark)	Disc diffusion assay	*Pseudomonas aeruginosa* ATCC 27852, *S. aureus* ATCC 25923, *Streptococcus pneumoniae, Cryptococcus neoformans* ATCC 66031, MRSA, *Candida albicans* ATCC 90028, *Trichophyton mentagrophyte* and *Microsporum gypseum*	Chloramphenicol (30 μg/mL) and fluconazole (25 μg/mL)	Methanol extract highly active towards *S. aureus* (MIC 0.073 mg/mL), *T. mentagrophyte* (MIC 0.039 mg/mL) and MRSA (MIC 0.156 mg/mL).Methanol and hexane extracts were inactive against *C. albicans and C. neoformans.*	Bii et al., (2010)
Methanol extract (leaves and bark)	β-Lactamase inhibitory activity	*β*-lactamases (TEM-1, IMP-1, OXA-10 and P99)	Nitrocefin (500 μM)	Percentage inhibition was 73.9%, 85.0%, 48.6% and 75.2%, against TEM-1, OXA-10, IMP-1, and P99 respectively.	Gangoué-Piéboji et al., (2007)
Aqueous methanolic extract (dried bark)	Disc diffusion assay	*Bacillus cereus, Proteus vulgaris, Salmonella typhi, Serratia marcescens and Escherichia coli*	Penicillin (500 mg/mL)	The greatest inhibition was observed towards *S. typhi (*zone of inhibition - ZI = 17.33 mm), followed by *P. vulgaris* (ZI = 16.67 mm) and *Serratia marcescens* (ZI = 16.67 mm), while *E. coli* and *Bacillus cereus* were the least susceptible.	Ngule et al., (2014)
Ethanol extract (stem-bark)	Disc diffusion assay	*Shigella dysenteriae*, *Shigella flexneri* – 2 strains and *Shigella boydii*	Chloramphenicol	The largest zone of inhibition was observed towards *S. boydii* and an MIC value of 2.625 mg/mL was recorded.	Dey et al., (2017)
Methanol extract (stem-bark) and β-sitosterol, benzoic acid, two oleanolic derivatives and *p*-hydroxybenzoic acid	Disc diffusion assay	*Staphylococcus aureus (ATCC25923), E. coli (ATCC25922);P. aeruginosa (ATCC27853); S.typhimurium (ATCC13311); Shigella flexneri (ATCC29903).*	Gentamycin (10 μg/mL)	The largest zone of inhibition was found observed towards *P. aeruginosa* (ZI = 21.03 mm), greater than gentamicin (ZI = 14.06 mm), followed by *S. flexineri* (ZI = 14.23 mm) and *S. aureus* (ZI = 11.10 mm). Pure compounds displayed moderate activity against the tested strains.	Deresa et al., (2022)
Antiviral activity					
Aqueous extract (stem-bark)	HIV-1 reverse transcriptase inhibition assay	*In vitro*	Foscarnet	Percentage inhibition was ≥50%.	Rukunga et al., (2002)
Aqueous extract (stem-bark)	Plaque inhibition assay	*In vitro*	Gancyclovir (5 μg/mL)	EC_{50} was recorded as 80 μg/mL.	Tolo et al., (2007)
Anti-oxidant activity					
Chloroform extract (dried bark)	Ferrous ion (Fe^{2+}) stimulated lipid peroxidation	*In vitro*	α-Tocopherol (Vitamin E)	Fractions and extract containing high concentrations of myristic acid (20 μg/mL) strongly inhibited lipid peroxidation in the microsomal preparations by 97%.	Hass et al., (1999)
Water and ethanol extracts (dried bark)	Hydroxyl scavenging activity	*In vitro*	Vitamin C (20, 40, 80, 160 mg/L)	Water extract was highly active (80%) compared to the ethanol extract (50%).	Steenkamp et al., (2006)

(*continued on next page*)

Table 3 (*continued*)

Extract/compound	Assay	Organism/Cell line	Positive control(s)	Activity	Reference
Ethyl acetate and methanol extracts (dried bark)	2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) assay	*In vitro*	Ascorbic acid	Inhibited DPPH radical scavenging activity.	Madivoli et al., (2018)
Aqueous extract (bark and leaves)	DPPH assay	*In vitro*	Ascorbic acid	70.2% free radical scavenging activity at 300 μg/mL.	Ssekatawa et al., (2022)
Antimutagenic activity					
Aqueous methanol (90%) and dichloromethane extracts (leaves and twigs)	AMES and VITOTOX® test	*Salmonella typhimurium* strain TA98 and TA 100 Strains TA104 RecN2-4 and TA104 pr1 of *S. typhimurium* in the presence and absence of S9 mix	4-nitroquinoline 1-oxide (4-NQO) And benzo[a] pyrene (B-[a]-P) (0.04 and 8 μg/mL)	No mutagenicity was observed.	Elgorashi et al., (2003)
Aqueous methanol (90%) and dichloromethane extracts (leaves and twigs)	AMES and VITOTOX® test	*Salmonella typhimurium* strain TA98 and TA 100,Strains TA104 RecN2-4 and TA104 pr1 of *S. typhimurium* in the presence and absence of S9 mix	4-nitroquinoline 1-oxide (4-NQO) and benzo[a] pyrene (B-[a]-P) (0.04 and 8 μg/mL)	No mutagenicity was observed.	Elgorashi et al., (2003)
Dichloromethane extract (twigs)	Ames test and micronucleus test	*Salmonella typhimurium* strain TA98	4-nitroquinoline 1-oxide (4-NQO) (0.4 ng/mL)	No mutagenicity was observed.	Verschaeve et al., (2004)
Antiproliferative and apoptotic activities					
Ethanol extract (dried bark)	Cancer cell lines (PC-3 and LNCaP cells) TRAMP mouse model	*In vitro* and *in vivo*	Camphotechin	Inhibited the growth of PC-3 and LNCaP cells; In TRAMP mouse model, a significant reduction was observed in prostate cancer incidence (35%) compared to casein fed mice (62.5%).	Shenouda et al., (2007)
Commercial *P. africana* extract (dried bark)	Immunofluorescence, proliferation assay, TUNEL assay	Stromal cells	NI	Downregulation of TGFB1 expression,FGF2 increased cells, DHT, VEGF and E2, decreased cell sensitivity	Quiles et al., (2010)
Dichloromethane extract (stem-bark)	Cell counting kit 8 cell proliferation assay	*In vitro*	Purified mouse IgG (10 μg/mL)	Downregulation of the expression of IL-7 mRNA (50 μg/mL)	Mwitari et al., (2013)
Commercial *P. africana* extract (dried bark)	5-Bromo-2′-deoxy-uridine (BrdU) incorporation assays	*In vitro*	Toxilight™ 100% Lysis	BrdU incorporation tests revealed that PA extract (5–100 μg/mL) inhibited proliferation of cultured human stromal cells stimulated by fetal calf serum, basic fibroblast growth factor, and epidermal growth factor.	Boulbès et al., (2006)
Ethanol extract (dried bark)	Mitogenic assay	Stromal cells	Staurosporine (1 nM)	*P. africana* extracts inhibited both stimulated and basal growth, with IC 50 values of 4.5, 7.7, and 12.6 μg/mL	Yablonsky et al., (1997)
Aqueous and methanol extracts (stem-bark)	MTT assay, acute oral toxicity study	Colon cancer (CT26.WT-ATCC® CRL-2638™) and breast cancer (4T1 ATCC® CRL-2539™) cell lines Swiss albino mice and towards Vero cells	Podophyllotoxin resin	Methanol extract was safe and effective with an average IC_{50} of 164.64 ± 4.14 μg/mL in the breast cancer cell lines and 21.33 ± 0.5 μg/mL in the colon cancer cell lines No indication of toxicity to Vero cells. There was no signs of acute toxicity after drug administration with LD_{50} of >5000 mg/kg body weight	Nabende et al., (2015)
Aqueous ethanolic (70%) extract (stem-bark)	Apoptosis and viability assays	PC-3 prostate cancer cells	Doxorubicin (1.13 μM)	Six-month-old micropropagated root extract was found to be lower (IC_{50} = 82.40 μg/mL) than the stem-bark extracts (IC_{50} = 52.30 μg/mL).	Komakech et al., (2022a)
Anti-asthmatic activity					
Aqueous extract (stem-bark)	Heart blood serum for ovalbumin specific immunoglobulin E (IgE) antibodies and quantification of eosinophil proportion in bronchoalveolar lavage fluid (BALF)	BALB/c mice	Chloroquine (100 μg/mL)	Extracts at 500 mg/kg body weight reduced the IgE and BALF eosinophil to 0.100 ± 0.0001 and 2.80 ± 0.20, respectively.	Karani et al., (2013)
Anti-androgenic activity					
Atraric acid (AA) ($C_{10}H_{12}O_4$ - 196.20) (isolated from the bark dichloromethane extract)	Inhibition of androgen receptor (AR).	*In vitro*	Commercial AA (10 μM)	Atraric acid inhibited the transactivation mediated by the ligand-activated human AR.	Papaioannou et al., (2009)
Dichloromethane extract (dried bark)	Androgen receptor responsive reporter gene assay	*In vitro*	Methyltrienolone ($3x10^{-10}$ μM)	Extract at 600 μg/mL inhibited androgen action at a very high level	Schleich et al., (2006a)
Atraric acid (AA) (isolated from the bark dichloromethane extract)	Androgen receptor responsive reporter gene assay	*In vitro*	Commercial AA (0.01, 0.1, 1, 10 and 100 μM)	Inhibition of AR function	Schleich et al., (2006b)

*NI – Not indicated.

Morphological identification of plant material is not sufficient for quality control of herbal medicines (Toniolo et al., 2014; Rohman et al., 2020). Therefore, rapid and accurate analytical approaches are essential for the authentication of herbal medicines and the detection of adulteration practices (Riedl et al., 2015; Wang and Yu, 2015).

The correct identification of medicinal plants is of the utmost importance in commercialisation of herbal drugs, since the inclusion of misidentified species, subspecies or varieties may result in products that are toxic or display poor or no efficacy (Efferth and Greten, 2012). The characteristic "cherry" odour released when the bark is crushed has been used for the identification of *P. africana*. However, the floral characteristics within the genus are similar, rendering this method unreliable for species verification (Stewart, 2003). Various deoxyribonucleic acid (DNA)-based technologies have complemented the methods of classical botany for plant identification. The DNA barcoding has become a powerful tool for the authentication of plants and is ideally suited to the QC of medicinal plants (Efferth and Greten, 2012). Chromatography techniques including thin layer chromatography (TLC), high performance thin layer chromatography (HPTLC), high performance liquid chromatography (HPLC), gas chromatography (GC) and capillary electrophoresis, are commonly used for the QC of medicinal plants, depending on the chemical properties of the compounds of interest. The relative simplicity of spectroscopy techniques has motivated researchers to investigate their use for the QC of herbal medicines. These techniques include nuclear magnetic resonance (NMR) spectroscopy, vibrational spectroscopy and hyperspectral imaging (Efferth and Greten, 2012; Huang, 2016).

9.2. Chromatography analysis

Various chromatograph methods have been used to isolate and analyse *P. africana* extracts. In many cases, the chromatographic instruments were hyphenated with a mass spectrometer. Hass et al. (1999) identified eleven constituents (myristic acid, palmitic acid, linoleic acid, oleic acid, stearic acid, arachidonic acid, *n*-docosonal, behenic acid, lignoceric acid, *β*-sitosterol, and ursolic acid) in crude *P. africana* (V-1326) extract and its fractions using GC coupled to a single flame ionization detector (FID).

Kadu et al. (2012) performed multivariate analysis of 20 populations of *P. africana* chloroform/methanol bark extracts using GC–MSD. The study investigated chemical diversity between and within samples from different populations by comparing the content of bioactive compounds (lauric acid, myristic acid, *n*-docosanol, ferulic acid, *β*-sitostenone, *β*-sitosterol and ursolic acid) present. The results revealed that the contents of many bark constituents were significantly correlated and *n*-docosanol concentration correlated significantly with all other compounds. The estimation of compound variations revealed the highest variation among populations for ursolic acid (66%) and the lowest for *β*-sitosterol (20%).

Mugaka et al. (2013) developed and validated an HPTLC method for *n*-docosanol and *β*-sitosterol quantification in the methanolic leaves and stem-bark extracts of *P. africana*. The results revealed that the leaves had higher *β*-sitosterol content ranging from 0.1518 to 0.2277 μg as compared to stem-barks ranging from 0.0969 to 0.2184 μg. On the other hand, *n*-docosanol was higher in leaves with content ranging from 0.3991 to 0.4989 μg as compared to stem-barks ranging from 0.1484 to 0.2069 μg. Thus, substituting the stem-barks with leaves in the preparation of herbal products seems to be a sustainable alternative, considering the high content of this bioactive compound in the leaves. Nyamai et al. (2015) conducted a phytochemical analysis of the essential oils of *P. africana* obtained through hydro-distillation, as well as hexane, DCM, methanol, and aqueous extracts using gas chromatography-mass spectrometry (GC–MS) and liquid chromatography coupled to mass spectrometry (LC–MS). The results revealed that the major compounds in the essential oils include myristic acid, linoleic acid, lauric acid, methyl myristate, methyl laurate and methyl linoleate using GC–MS. Campesterol, *β*-sitosterol, lup-20 (29)-en-3-one, palmitic acid, *β*-sitostenone, (3*β*,5*α*)-stigmast-7-en-3-ol, stigmastan-3,5-diene, and *α*-tocopherol were identified in both the hexane and DCM extracts using GC–MS. The analysis of methanol and aqueous extracts using LC–MS revealed the presence of procyanidin B5, feruloyl-quinic acid, robinetinidol-(4-*α*-8)-catechin-(6-α)-robinetinol, prunetrin, quercetin3,3′-dimethylether-4′-glucoside, cyanidin-*O*-galactoside, chlorogenic acid, ursolic acid, isochamaejasmin+, cinnamtannin A2, isoliquiritin, and cyanidin-3-*O*-rutinoside. Three compounds were identified from the combination of hexane and dichloromethane leaf and bark extracts using GC–MS, including *β*-sitosterol, *β*-amyrin and *β*-sitosterol-3-*O*-glucoside (Maiyo et al., 2016). Recently, Komakech et al. (2022b) investigated the phytochemical profiles of methanolic *P. africana* stem-bark extracts using GC–MS and LC-ToOF–MS. The presence of 32 components was revealed by the GC–MS, including β-sitosterol, benzoic acid, 3,4-altrosan, 4-(hydroxymethyl)-2,6-dimethoxyphenol, catechol, 3-furanmethanol, vanillic acid, oleic acid, 6-hydroxy-5-trifuoromethylcyclohexa-1,3-diene, 4H-pyran-4-one,2,3-dihydro-3,5-dihydroxy-6-methyl-, isopropyl myristate, 9-octadecenamide, 2,6-dimethoxy-, 4-hydroxy-3-methoxybenzaldehyde, 5-hydroxymethyl-2-furaldhyde, 13-docosenamide, (Z)-, benzoic acid, methyl ester, benzoic acid, 4-hydroxy-3,5-dimethoxy-, mandelamide, squalene, 4-vinylphenol, n-hexadecanoic acid, (E)-4-(3-hydroxyprop-1-en-1-yl)-2-methoxyphenol, 9,12-octadecadienoic acid (Z,Z)-, isosorbide, sorbitol, phenol, octadecanoic acid, benzyl, β-d-glucoside, (Z)-, (R)-α-(β-Dglucopyranosyloxy) benzeneacetonitrile, benzenepropanol, 4-hydroxy-3-methoxy-, benzaldehyde, 4-hydroxy-3,5-dimethoxy-, 4-(hydroxymethyl)-2,6-dimethoxyphenol, and dihydroxyacetone. *Prunus africana* methanolic extracts contained a variety of phytochemicals that were detected using LC-TOF–MS analysis. Among them, betulonic acid, luteoloside, astragalin, naringenin, chlorogenic acid, pedunculoside, coproporphyrin I, guanosin, hyperin, hexadecanedioic acid, and Mesoporphyrin IX.

9.3. Vibrational spectroscopy analysis

Vibrational spectroscopy is used to describe collectively the techniques of mid-, near- and far-infrared (IR), as well as Raman spectroscopies (Stuart, 2004). It provides important information about the structure of the molecules, their symmetry and the nature and strength of bonds. It is a very powerful technique for the characterization of organic functional groups and hydroxyl coverage with several advantages over conventional analytical techniques (Hadjiivanov et al., 2021).

Begeno (2020) investigated the phytochemical characterisation of the root bark sequentially extracted with hexane, ethyl acetate and methanol using spectroscopy techniques such as IR and NMR. The results revealed that AYU, a compound obtained through characterization, had in the IR spectrum, an absorbance band at 3400 cm^{-1} showing the O–H stretching that indicated the presence of a hydroxyl group. The strong absorption band was at 2922 cm^{-1} showing the presence of the C–H stretching of the olefinic group. Madivoli et al. (2018) evaluated the anti-oxidant activity of crude methanolic stem-bark extracts of *P. africana* and *Harrisonia abyssinica* using the DPPH assay. The results of the study revealed the presence of secondary metabolites which were further confirmed by FT-IR and characterisation that revealed the presence of various bioactive functional groups such as OH, NH, CHO, COOH and –COOR.

10. Commercial aspects

The increasing demand for traditional and alternative medicines has been linked to adverse socio-economic conditions in developing countries, as well as to a growing international commercial market for herbal products, particularly those with regulatory approval for medicinal

claims, such as *P. africana* with evidence for efficacy in the treatment of micturition disorders associated with BPH (Bodeker et al., 2014, European Medicines Agency, 2015; Cunningham et al., 2016). *Prunus africana* products are marketed both directly and online, with many new patent applications filed for solid and liquid dosage forms globally between 1985 and 2002 (Cunningham, 2014a,b). Commercial harvest and trade of *P. africana* bark were initiated in Cameroon with a small operation of only 10 tons, when Plantecam started harvesting in the West and Northwest regions (Cunningham et al., 1997). In 2000, the World Agroforestry Centre published a monograph indicating the use of *P. africana* preparations for the treatment of symptoms associated with mild and moderate BPH, as well as for chronic prostatis and for genital infection. Furthermore, extracts were recommended for use in amnesia due to hypoxia, bladder dysfunction secondary to BPH, sexual disorders, and idiopathic hirsutism in men and women (Hall et al., 2000; Pagano et al., 2014).

More than 23 different western pharmaceutical companies market products prepared from *P. africana*, and these include Madaus (Germany), Indena Spa and Inverni Della Buffa (Italy), Prosynthèse and Laboratoires Debat (France). This demand was predicted to double, or even triple, within the first decade of the 21st century, due to aging populations and growing confidence in herbal remedies in the major consumer markets in Europe and North America. This translated into a projected demand of 7000–11000 tons of bark entering the market annually. The traditional demand for bark within Africa, based on household surveys (Cunningham et al., 1997) is estimated to be as much as 500 tons per year. Roughly, 2000 tons of bark were harvested from Cameroon in 1992 alone, the bulk of which was sold to European markets (Cunningham and Mbenkum, 1993). By 1997, *P. africana* had an estimated annual OTC value of close to US $220 million worldwide (Cunningham et al., 1997). At that time, the two countries of Cameroon and Madagascar were responsible for supplying up to 60% of the demand, or roughly 3200–4900 tons of the bark annually (Ingram et al., 2009).

In 1972, the company Laboratoires Debat started the Plantecam facility in Mutengene, Cameroon to assist with the export of *P. africana* bark from that country. It was later sold to the French company, Groups Fournier, in the early 1990s (Cunningham and Cunningham, 2000), and large-scale export continued. Fournier Pharma became a major player in the marketing of *P. africana*. Tadenan® is their best-known *P. africana* product and is sold in several countries in Europe and elsewhere (Cunningham, 2014a,b). Indena S.p.A of Italy distributes *P. africana* products to more than 40 countries globally (Cunningham, 2014a,b).

Plantecam initially had a monopoly on the harvesting of *P. africana* bark. However, after 1985, 50 licenses for harvesting were extended to entrepreneurs in the country, and it became more difficult to regulate the volumes (Ndibi and Kay, 1997). The Cameroon Forest Administration granted harvesting permits to 33 trade companies in 2005, which sanctioned the harvesting of 2558 tons of *P. africana* and in 2006, 1260 tons were harvested. These volumes were recorded on a national database on trade forest products (Betti and Ambara, 2013).

Continued concerns about overexploitation and sustainability resulting from commercial trade, resulted in the European Union banning the importation of the stem-bark from Cameroon in 2007. Nevertheless, the country remained the largest exporter of this natural resource from Africa. The popularity of the commodity declined after CITES recommendations resulted in the suspension of trade from the Democratic Republic of the Congo, Tanzania and Equatorial Guinea (CITES, 2009). No import quotas were issued from Burundi, Cameroon, Togo, Madagascar and Uganda in 2009.

Cunningham concluded, in the discussion on bark use management and commerce in Africa, that cultivation is suggested as a possible solution to the current over-harvest of the species from the wild and that the transition to agroforestry is essential as wild harvest is only a short-term solution to the provision of this commodity on a large-scale (Cunningham, 2014a,b).

11. Conclusions

Prunus africana is one of the most precious medicinal plants in the African continent and a highly commercialised indigenous plant used by thousands to manage various disease conditions. Its bark is exported to Europe where it is formulated into capsules, tablets, and liquid extracts as herbal medicine to treat mainly lower urinary tract symptoms and micturition disorders associated with BHP (European Medicines Agency, 2015).

The investigation of the phytochemistry of the plant has led to the isolation of constituents including phytosterols and other substances such as phenols, triterpenes, fatty acids, and linear alcohols, which may play a role in the therapeutic outcomes. The extensive use of *P. africana* in traditional medicine has been substantiated by scientific studies that have shown that it exhibits biological activities such as anti-inflammatory, anticancer, antiviral, and antimicrobial effects (Catalano et al., 1984; Bombardelli and Morazzoni, 1997). Reviews of the clinical trials on *P. africana* have shown its potential long-term effectiveness and possible ability to prevent complications associated with BPH (Ishani et al., 2000).

However, new methodological strategies to the existing clinical trials have to be developed for further high-quality evidence on standardised and characterised products to provide definitive clinical evidence of safety and efficacy.

Since 1960, Jacques Debat, was introduced to *P. africana* bark by Zulu men in the Vryheid area of KwaZulu-Natal (South Africa) as a remedy to treat difficulties in passing urine, then afterwards, its potential wider use to treat benign prostatic hypertrophy resulted in its patenting in early 1966 and stimulated the trade we know today. The plant has become an important African product traded internationally and is contributing to the health and well-being of thousands of people from its original habitat in Cameroon and elsewhere. Further investigations of the BPH treatment and anti-inflammatory activity need to be undertaken to confirm the ethnobotanical claims matching these activities.

Funding

The National Research Foundation, grant number 86923, South Africa Medical Research Council, EMU grant number 23015, and the Tshwane University of Technology are acknowledged for funding the project.

CRediT authorship contribution statement

Emmanuel Rubegeta: contributed to the phytochemistry and biological activity aspects. **Felix Makolo:** contributed to the phytochemistry and biological activity aspects. **Guy Kamatou:** contributed to the phytochemistry and biological activity aspects. **Gill Enslin:** contributed to the phytochemistry and biological activity aspects. **Sushil Chaudhary:** performed the bibliometric analysis and compiled the content. **Maxleene Sandasi:** performed the bibliometric analysis and compiled the content. **Anthony B. Cunningham:** contributed to sections on conservation, sustainable use and genetics and produced Figures 5, 7, 8 and 9, while. **Alvaro Viljoen:** conceptualised the review and completed the final proofreading.

Declaration of competing interest

The corresponding author (AM Viljoen) declares his role as Editor-in-Chief of the Journal of Ethnopharmacology. The review process was handled by an associate editor of the journal.

Data availability

No data was used for the research described in the article.

Acknowledgements

Our appreciation is extended to Sandra Burrows, who prepared the botanical illustration for the publication and for some of the photographs, Van Wyk, A.E. (Fig. 5B and C) and the late Arthur Stevens (Fig. 8B). AB-C would also like to thank Ayuk, E., Besong, S., Franzel, S., Kale, C., Leakey, R., Mbenkum, F.E., Nkuikeu, R., Tchouto, P., Stenmanns, T. and Sunderland, T. for their insights into *P. africana* during fieldwork.

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