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REVIEW

Traditional uses, phytochemical and pharmacological properties of *Feretia apodanthera* Del. (Rubiaceae): a literature review

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Abstract

Feretia apodanthera Delile (Rubiaceae) is a plant found mainly in tropical Africa. In this region, the different parts of *Feretia apodanthera* Delile (roots, bark, leaves, fruits) are used as traditional remedies in human medicine. Its uses are diverse and include infectious, metabolic and neurological diseases. The objective of this review was to explore the pharmacological activities, chemical constitution and to give an overview of the traditional medicinal uses of the plant. A search for relevant articles on the subject was carried out in the Scopus, Science Direct and PubMed bibliographic databases. In traditional medicine, *Feretia apodanthera* Del. has therapeutic potential for treating various conditions such as malaria, hypertension, diabetes, pain, epilepsy, mental disorders, abdominal pain, wounds, fibroids, urinary tract infections, vomiting, dysentery, headache, constipation, hepatitis, dermatoses. Studies have made it possible to isolate and describe the chemical formula of certain phytochemicals contained in the plant, in particular the iridoid glucosides. *Feretia apodanthera* Del. extracts have various pharmacological activities such as anti-epileptic, antibacterial, antimalarial, antioxidant and anti-diabetic activity. Regarding toxicity, data are limited so far and studies need to be conducted for a better exploration of it. Although *Feretia apodanthera* Del. has been used extensively in traditional medicine, there is still a lack of pharmacological studies. Based on the ethnopharmacological data, more chemical and pharmacological studies are needed to refine the knowledge on the active principles underlying the uses of the plant in traditional medicine. Similarly, the toxicological profile of the plant should be clearly established for safe use as a phytomedicine.

Keywords *Feretia apodanthera* · Ethno-medicinal use · Phytochemistry · Pharmacology · Toxicology

Introduction

The use of natural substances and particularly medicinal plants has increased significantly worldwide over the last two decades (Bareetseng 2022; Ekor 2014). The global herbal medicines market, estimated at US$ 135 billion in 2022, is expected to reach US$ 178.4 billion by 2026, with an annual growth rate of 8.1% (Global Industry Analysts 2022). Today, herbal medicines and plant-derived drugs are the main source of primary health care for 80% of the world's population (OMS 2013). Due to their ethno-medicinal use, medicinal plants and their biologically active compounds have attracted the attention of many researchers to develop new, effective and safe drugs. As a result, the scope of application of herbal medicines has expanded considerably and is moving towards the treatment of life-threatening diseases such as cancer, diabetes, hypertension and infectious diseases (Alhazmi et al. 2021; Atena Mahdavi et al.

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2021; Buyel 2018; Hussain et al. 2020; Mohammadi et al. 2020; Odukoya et al. 2021; Salehi et al. 2019).

The Rubiaceae family is characterised by the production of bioactive metabolites with high pharmacological potential (Martins and Nunez 2015). Rubiaceae is a family of flowering plants containing 630 genera and over 13,000 species, many of which are found in tropical or subtropical regions (Chaniad et al. 2022; Karou et al. 2011). Several plants of this family are used in traditional medicine (TM) to treat many conditions, such as dysentery, constipation, fever, anaemia, malaria, dermatoses, syphilis, gonorrhoea, epilepsy, dementia, diabetes and hypertension (Karou et al. 2011).

Feretia apodanthera Del. a widespread savannah shrub in tropical Africa (Bailleul et al. 1977) is one such plant. Different parts of the plant are used to treat epilepsy, mental disorders, abdominal pain, urinary tract infections, vomiting and headache (Taiwe et al. 2015). In addition to its traditional use, in vitro and in vivo pharmacological studies have indicated the potential activity of *Feretia apodanthera* Del. extracts as antimalarial, antiepileptic, antioxidant, antibacterial and anticancer agents (Ancolio et al. 2002; Coulibaly et al. 2014; Pesca et al. 2013; Taiwe et al. 2015a). Due to the recognized potential medicinal value of *Feretia apodanthera* Del. an increasing number of phytochemical investigations have been conducted. Chemical analysis of extracts from different parts of the plant revealed the presence of various bioactive compounds belonging to several phytochemical classes such as flavonoids, alkaloids, tannins and quinones (Njimoh et al. 2018; Sangaré, 2003; Taiwe et al. 2015a). The plant also contains numerous iridoid glycosides, some of which have been isolated and are believed to be responsible for certain activities of the plant (Bailleul et al. 1980; Taiwe et al. 2016).

The objective of this review was to explore the pharmacological potential of *Feretia apodanthera* Del. and the phytochemicals extracted from it. It specifically addresses the traditional uses, phytochemistry, pharmacology and toxicology of *Feretia apodanthera* Del.

Methods

It consisted of a literature review on the traditional uses and phytochemical and pharmacological properties of *Feretia apodanthera* Del. To this end, a search of relevant articles on the subject was carried out in the Scopus, Science Direct and PubMed bibliographic databases. The search considered articles published until 31 December 2022, in English or French. The keyword equations used to retrieve articles from the bibliographic databases were "*Feretia apodanthera* AND traditional uses", "*Feretia apodanthera* AND phytochemistry", "*Feretia apodanthera* AND pharmacological activities", "*Feretia apodanthera* AND toxicity". The structures of the compounds were drawn with ChemDraw version 8.0.

Botany and traditional uses

Taxonomy

According to the World Flora Online (WFO), *Feretia apodanthera* Delile is the only accepted name for the plant, with two synonyms: *Canthium elliptic* Hochst. ex Delile and *Pavetta elliptic* Hochst (WFO (The world flora online), n.d.). There are also three infraspecific taxa of the species *Feretia apodanthera* Delile: *Feretia apodanthera* subsp. Apodanthere, *Feretia apodanthera* subsp. keniensis Bridson et *Feretia apodanthera* subsp. tanzaniensis Bridson (WFO).

The taxonomic hierarchy of the plant is presented in Table 1.

Vernacular names in Africa

Feretia apodanthera Del. has different names in different countries and languages, as local people easily recognise plant species with vernacular names rather than with Latin binomial names. The vernacular names of the plant are presented in Table 2.

Botanical description

Feretia apodanthera Del. is a shrub 2 to 3 m high, rarely more, with numerous upright, tangled branches. It has oval-elliptic leaves, mucronate at the top, up to 6 cm long and 3 cm wide, but usually less, pubescent on the veins on the lower side (Kerharo and Adam 1964). The flowers are white or pinkish, very fragrant, clustered at the tip of the shoots, appearing especially in the dry season when the plant is

Table 1 Taxonomy of *Feretia apodanthera* Del.

Kingdom	Plantea
Subkingdom	Eukaryotes
Phylum	Spermaphytes
Subphylum	Angiosperms
Class	Dicotyledons
Order	Gentianales
Family	Rubiaceae
Genus	Feretia
Species	*Feretia apodanthera* Delile
Subspecies	*Feretia apodanthera* subsp. apodanthere
	Feretia apodanthera subsp. keniensis
	Feretia apodanthera subsp. tanzaniensis

Table 2 Common names of *Feretia apodanthera* Del. in different African countries and languages

Country	Language	Local name	References
Benin	Bariba	Tounbounya	(Adjanohoun et al 1989)
Burkina-Faso	Moré	Poinr-komga, parwiiga Kitinga, kitga, firedga	(Nadembega et al. 2011) (Odile Nacoulma, 1996)
	Fulani	Burudehi	(Lykke et al. 2004)
Mali	Dogon	Diguiri	(Sangaré, 2003)
	Bambara	Tusigi	(Denis Malgras 1992)
	Malinké	Jula sungalani	(Denis Malgras 1992)
	Minyanka	Cèlère kapinge	(Denis Malgras 1992)
	Sénoufo	Ntyurungo	(Denis Malgras 1992)
	Bobo-fing	Tiefile	(Denis Malgras 1992)
	Bamanan	Djourasounkala	(Diarra et al. 2016)
Mauritania	Peulh	Commbi	(Abou Sidi 1982)
Niger	Haussa	Kuru kuru	(Adam et al. 1972)
	Zarma	Fifirdji	(Adjanohoun et al 1980)
Nigeria	Haussa	Kuru-kuru	(Hussain and Karatela 1989)
Senegal	Peul	Tobida	(Kerharo and Adam 1964)
	Toucouleur	Tobi	(Kerharo and Adam 1964)
Tanzania	Gogo	Mpakapaka	(Ruffo et al. 2002)
Togo	Yanga	Sitindakuan	(Adjanohoun et al 1986)
	Moba	Nassisolok	(Adjanohoun et al. 1986)
	Adja	Vévêî	(Adjanohoun et al. 1986)

leafless; the calyx is pinkish. The fruits, 3 to 7 mm in diameter, are small globular berries with persistent sepals at the top. Flowering occurs from April to May before or at the beginning of foliage. The fruits ripen from August to October. (Dalziel, H.M; Burkill, 1937; Denis Malgras 1992; Kerharo and Adam 1964).

Geographic distribution

Feretia apodanthera Del. is a widespread savannah shrub in tropical Africa (Bailleul et al. 1977). It is distributed along tropical Africa from Mauritania to Nigeria and across the Congo basin to Sudan and East Africa (Owolabi et al. 2020). It is mainly found in clay soils and on termite mounds (Kerharo and Adam 1964).

Figure 1 shows the geographical distribution of the *Feretia apodanthera* Del. species.

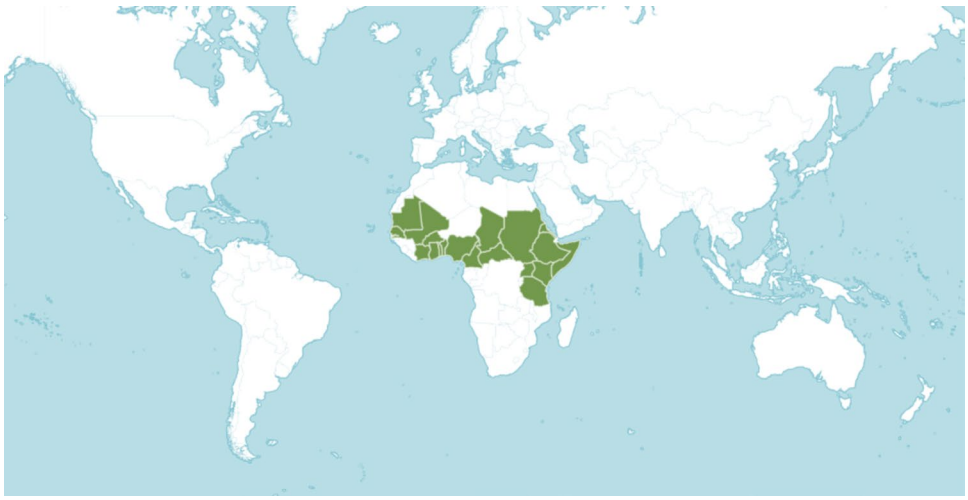


Fig.1 Geographic distribution (https://powo.science.kew.org/) (Plants of the World Online, n.d.)

Ethnopharmacology

The different parts of *Feretia apodanthera* Del. are used for various medical applications. These different uses in TM are summarised in Table 3.

Phytochemistry

Preliminary phytochemical studies of aqueous, methanolic and chloroform extracts of leaves and stem barks of *Feretia apodanthera* Del. revealed the presence of tannins, coumarins, cardiotonic heterosides, reducing compounds, mucilages. Alkaloids as well as flavonoids were found only in the

Table 3 Ethnomedical uses of *Feretia apodanthera* Del.

Plant part	Medecinal use	Preparation method	Administration route	Country and references
Root	Miscarriage	Decoction	Oral	
	Urethritis, adenitis, nephropathy	Decoction	Oral, bath	Senegal (Mathieu et al. 2021)
	Infected wounds	Dried root bark powder added to water	Local	Senegal (Mathieu et al. 2021)
	Malaria	Root and bark decoction	Oral, bath	Mali (Inngjerdingen et al. 2004)
	Dysentery	Decoction	Oral	Mali (Sangaré, 2003)
	General tiredness	Maceration	Oral	Mali (Sangaré, 2003), Niger (Adam et al. 1972)
	Gonorrhoea	Decoction	Oral	Niger (Adam et al. 1972)
	High blood pressure	Decoction	Oral	Niger (Adam et al. 1972)
	Stomach ache	Decoction	Oral	Tchad (Nguemo Dongock et al. 2018)
	Hepatitis	Decoction	Oral	Nigeria (Hussain and Karatela 1989), Mali (Denis Malgras 1992), Burkina-Faso (Nadembega et al. 2011)
	Diabetes	Decoction or infusion of root and leaves	Oral	Burkina-Faso (Fernandez de la Pradilla 1988)
	Fibroma, cyst	NP[§]	Oral	Burkina-Faso (Souleymane et al. 2020)
	Aphrodisiac	Maceration	Oral	Burkina-Faso (Adjanohoun et al 1989)
Bark	Epilepsy, anxiety, convulsion, headache, insomnia, schizophrenia, pain	NP[§]	NP[§]	Burkina-Faso (Nadembega et al. 2011)
Leaves	Urinary tract infections	NP[§]	NP[§]	Cameroun (Arbonnier 2000; Taiwe et al. 2015b)
	Malaria	Decoction	Oral, bath	Senegal (Adam, 1974)
	Pain due to sickle cell disease	Decoction	Oral, bath	Mali (Diarra et al. 2015)
	Otitis	Crushed leaf juice	Auricular	Mali (Danton et al. 2019)
	Scorpion bites	NP[§]	Scarification	Mali (Denis Malgras 1992)
	Snake bites	Juice (crushing)	NP[§]	Burkina-Faso (Fernandez de la Pradilla 1981)
	Headaches	Decoction	Oral and local	Burkina-Faso (Nadembega et al. 2011)
Leafy stem	Stomach ache	Decoction of leafy stem and roots	Oral	Togo (Adjanohoun et al. 1986)
	Conjunctivitis	Decoction	Eye instillation	Mali (Denis Malgras 1992)
	Fortifying	NP[§]	Bath	Mali (Denis Malgras 1992)
	Dermatosis	NP[§]	Local	Mali(Denis Malgras 1992)
	Laxative	Decoction	Oral	Togo (Adjanohoun, et al., 1986) Benin (Adjanohoun et al 1989)
	Diabetes	Decoction	Oral	Togo (Holaly et al. 2015)

[§]Not specified

barks and saponosides in the leaves (Sangaré, 2003). The aqueous extract of stem bark collected in Cameroon showed the presence of flavonoids, alkaloids, saponosides, tannins, glycosides, anthraquinones and phenols (Njimoh et al. 2018; Taiwe et al. 2015a). A qualitative phytochemical analysis of carbohydrates, free reducing sugars, anthracene derivatives, cardiotonic glycosides, saponosides, tannins, flavonoids, alkaloids, unsaturated sterols and triterpenes was carried out on n-hexane, diethyl ether, ethanol and water extracts of *Feretia apodanthera* Del. The results showed the presence of unsaturated sterols and triterpenes in all four extracts. Tannins, flavonoids and cardiotonic glycosides were present in the diethyl ether, ethanol and water extracts; reducing sugars and saponosides were present only in the ethanolic and water extracts. The ethanolic extract contained alkaloids. Free anthraquinones were absent in all four extracts (Owolabi et al. 2018).

The chemical constituents of *Feretia apodanthera* Del. were analysed quantitatively. The study of the phenolic compound content of aqueous and ethanolic extracts of the plant's root barks revealed a predominance of tannins. Indeed, flavonoid contents of 10.90 ± 0.05 and 3.30 ± 0.42 mg QE (Quercetin Equivalent) /100 g of dry extracts were found in each extract, respectively. For hydrolysable tannins, the contents were respectively 4.62 ± 0.08 and 18.43 ± 0.08 mg TEA (Tanic Acid Equivalent) /100 g dry extract. Condensed tannins were present at 468.60 ± 4.32 and 52.60 ± 0.23 mg EAT (Equivalent Tannic Acid) /100 g dry extract, respectively (Souleymane et al. 2020). The total phenolic compounds of aqueous and hydro-acetone extracts of aerial parts (stem bark) of *Feretia apodanthera* Del. were assayed. Also, the β-carotene content was determined. The aqueous extract contained 12.81 ± 0.14 mg Gallic Acid Equivalents (GAE)/100 g dry extract and 1.34 ± 0.04 mg Gallic Acid Equivalents (GAE)/100 g dry extract of polyphenols and flavonoids, respectively, as well as 0.220 ± 0.03 mg/g dry extract of β-carotene. The polyphenols and flavonoids had respective contents of 28.36 ± 0.57 mg Gallic Acid Equivalents (GAE)/100 g dry extract and 3.58 ± 0.19 mg GAE/100 g Gallic Acid Equivalents (GAE)/100 g dry extract in the hydro-acetone extract. The β-carotene content was 0.57 ± 0.001 mg/g dry extract c (Coulibaly et al. 2014).

A number of organic compounds have been isolated and identified from *Feretia apodanthera*, Del. including iridoids.

From the stem bark and flowers of the plant, eight iridoid glycosides have been isolated and identified, including feretoside, gardenoside, geniposide, desacetyl-asperulosic acid, 11-methyl ixoside, apodanthoside, 10-ethyl apodanthoside and apodanthoside penta-acetate. Only feretoside, gardenoside and apodantheroside penta-acetate were present in the flowers (Bailleul François, Pierre Delaveau, 1980).

Carbon-13 proton nuclear magnetic resonance (NMR) spectroscopy was used to elucidate the chemical structure of iridoid glycosides isolated from stem barks and flowers of *Feretia apodanthera* Del. These were feretoside, gardenoside, geniposidic acid, apodanthoside and deacetylasperolosidic acid (Table 4) (Bailleul et al. 1977; Taiwe et al. 2016).

Fourier transform infrared spectroscopy and gas chromatography-mass spectroscopy (GC–MS) analysis were used to identify the bioactive compounds present in ethanolic extracts of *Feretia apodanthera* Del. root bark. Among the bioactives isolated and described were Pentan-2-one, methyl ester hexadecanoic acid, trans-9-octadecenoic acid, pentylester, methyl cyclohexanepropionate, palmitoleic acid, 10-indecenoyl chloride. These compounds are thought to be potential anti-inflammatory agents (Owolabi et al. 2018).

Pharmacological activities

Different pharmacological activities of *Feretia apodanthera* Del. have been demonstrated in experimental studies. The extracts of *Feretia apodanthera* Del. possess various biological and pharmacological activities, such as antimalarial, antiepileptic, anticonvulsant, antioxidant, anticancer, anti-inflammatory, antidiabetic and many other properties. The pharmacological activities are summarised in Table 5.

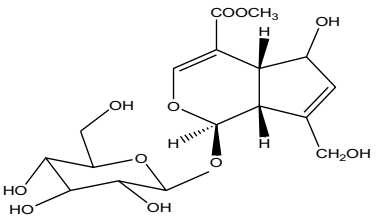
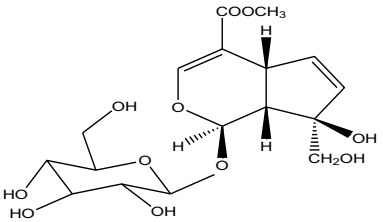
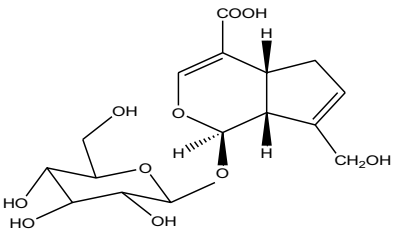
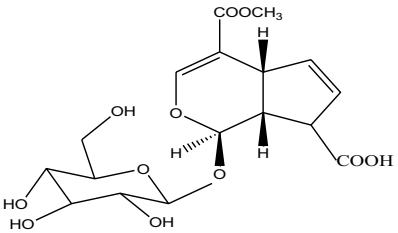
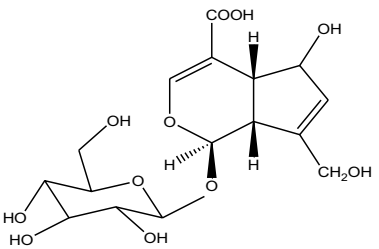
Antiepileptic activity

The antiepileptic activity of a lyophilized aqueous extract of *Feretia apodanthera* Del. stem bark was evaluated in mice excited with pentylenetetrazole (PTZ) at 30 mg/kg. Administration of the extract at doses of 150 and 200 mg/kg significantly increased the latency of myoclonic jerks, clonic seizures and generalised tonic–clonic seizures. This seizure protection offered by *Feretia apodanthera* Del. at 200 mg/kg was comparable to that of the reference antiepileptic drug, sodium valproate (300 mg/kg) (Taiwe et al. 2015a).

Anticonvulsivant activity

Iridoid glycosides isolated from the stem bark of *Feretia apodanthera* Del. were evaluated for anticonvulsant activity in mice. Murine models of generalised tonic–clonic seizures induced by 2.7 mg/kg bicuculline or 70 mg/kg PTZ were used. Iridoid glycosides at doses of 30 and 90 mg/kg protected mice from bicuculline-induced motor seizures in all pre-treated animals. Behavioural seizures and mortality induced by pentylenetetrazole at 70 mg/kg were strongly antagonised by the moieties. Complete protection against

Table 4 Chemical structures of iridoid glycosides isolated from stem barks and flowers of *Feretia apodanthera* Del.(Taiwe et al. 2016)

Compound name	Chemical structure
Feretoside	
Gardenoside	
Geniposidic acid	
Apodanthoside	
Desacetylasperolosidic acid	

mortality was achieved at 60 and 90 mg/kg (Taiwe et al. 2016).

Anxiolytic activity

Aqueous extracts of *Feretia apodanthera* Del. stem bark were tested for anxiolytic activity in mice by the Elevated Cross Maze (EPM) test and the Open Field Test (OFT). Aqueous extract of *Feretia apodanthera* Del. at the dose of 200 mg/kg showed anxiolytic activity in the elevated cross maze test by increasing the number of entries in the open arms, the percentage of entries in the open arms, the ratio of open entries/total entries versus closed entries/total entries and by reducing the number of entries in the closed arms and the percentage of time in the closed arms. This anxiolytic activity of *Feretia apodanthera* Del. was confirmed in the OFT by increasing crossings, grooming and time spent in the centre (Taiwe et al. 2015a).

Antioxydant activity

An aqueous decoctate of *Feretia apodanthera* Del. leafy twigs and its hydro-acetone fraction exhibited antioxidant activity. The antioxidant activity of the extracts was

Table 5 Synopsis of pharmacological activities of *Feretia apodanthera* Del

Pharmacological activity	Extract	Part use	Model	Living system/organ/cell tested	Result	Reference
Antiepileptic	Aqueous	Stem bark	PTZ test	Swiss mouse	Improvement in seizure score and decrease in the number of myoclonic jerks	(Taiwe et al. 2015a)
Anxiolytic	Aqueous	Stem bark	The Elevated Cross Maze (EPM) and the open field test	Swiss mouse	Increased number and percentage of entries into open arms, ncrease in crossings, grooming and time spent at the centre	(Taiwe et al. 2015a)
Anticonvulsivant	Fraction (Iridoid glycosides)	Stem bark	Bicuculline and pentylenetetrazole test	Swiss mouse	Decreased duration of seizures and mortality	(Taiwe et al. 2016)
Antioxydant	Aqueous and hydro-acetonic fraction	Leafy sprig	ABTS, DPPH, FRAP	–	Good antioxydant activity of hydro-acetonic fraction	(Coulibaly et al. 2014)
	Aqueous, ethanolic, hexanic, etheric	Root bark	DPPH	–	The percentage of free radical scavenging activity of all these extracts was significantly lower than that of vitamin C	(Owolabi et al. 2018)
Anti-inflammatory	Ethanolic and purified fractions	Root bark	Carrageenan-induced paw edema	Albino rats	Inhibition of oedema	(Owolabi et al. 2020)
	Aqueous, ethanolic,Hexanic, etheric	Root bark	Carrageenan-induced paw oedema	Albino rats	Higher anti-inflammatory potential than standard at 4th and 5th hour	(Owolabi et al. 2018)
Antimalaria	Methanolic	leaves	-	D6 and W2 *plasmodium falciparum* strain	Active on W2 strain	(Ancolio et al. 2002)
Antibacterial	Aqueous, hydro-acetonic, fractions	Bark and leaves	Agar diffusion and liquid micro-dilution	*Bacillus licheniformis, Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa et Staphyloccocus aureus*	Hydro-acetone extract active on all strains. Aqueous extracts active on *Escherichia coli*, *Bacillus licheniformis* and *Staphyloccocus aureus*. Active fractions on *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*	(Coulibaly et al., 2019)
	Aqueous, alcaloidic fraction	Stem bark	Agar diffusion and liquid micro-dilution	*Staphylococcus aureus*, *Escherichia coli*, *Proteus vulgaris*, *Providencia stuartii* et *Pseudomonas aeruginosa*	Extracts and fractions active on all strains	(Njimoh et al. 2018)
Antiangiogenic	Methanolic	Aerial parts	Elisa test	Interfering in the recognition of VEGFs/VEGFR-1 (Flt-1) by VEGF family members	Inhibition of VEGFs/Flt-1 interaction	(Pesca et al. 2013)

Table 5 (continued)

Pharmacological activity	Extract	Part use	Model	Living system/organ/cell tested	Result	Reference
Anti-diabetic	Aqueous decoctate, hydro-acetonic macerate	Stem bark, leaves	α-amylase and α-glucosidase inhibition	-	Significant inhibitory activity of hydro-acetone extract on α-amylase and α-glucosidase	(Coulibaly et al. 2020)
Cytotoxicity	Methanolic macerate and fractions	Leaves	Flow cytometry	THP1	Cytotoxicity significant for the macerate and not significant for the fractions	(Ancolio et al. 2002)
	Aqueous, alkaloidic fraction	Stem bark	MTT	3T3	Cytotoxicity not significant for the aqueous extract and significant for the fraction	(Njimoh et al. 2018)

evaluated using their ability to scavenge 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical activity, reduce ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}) (FRAP) and reduce 2, 2'- azino bis-(3-ethylbenzothiazoline-6-sulfonic acid) cationic radical (ABTS). The hydro-acetone fraction showed the most potent antioxidant activity for all methods. The 50% inhibitory concentrations (IC_{50}) were 5.96 ± 0.24 µg/ml, 11.90 ± 2.67 µg/ml, and 51.02 ± 2.74 µg/ml for the ABTS, DPPH and FRAP methods respectively (Coulibaly et al. 2014).

Furthermore, the antioxidant activity of *Feretia apodanthera* Del. root bark was evaluated. Several extracts were prepared by maceration of the bark powder in different solvents including n-Hexane, diethyl ether, ethanol and water. The antioxidant activity of the plant extracts was evaluated in vitro using their ability to scavenge the free radical activity of stable 1,1-diphenyl-2-picrylhydrazyl (DPPH). The results showed that the ethanolic extract had the lowest inhibitory concentration 50% (IC_{50}) (0.053 mg/ml), followed by the aqueous extract (0.063 mg/ml), the n-hexane extract (0.7499 mg/ml) and the diethyl ether extract (1.296 mg/ml). The percentage free radical scavenging activity of all these extracts was significantly higher than that of vitamin C with an IC_{50} of 0.048 mg/ml (Owolabi et al. 2018).

Anti-inflammatoiry activity

The anti-inflammatory activity of ethanolic extracts of *Feretia apodanthera* Del. root bark and nine fractions obtained by partial purification of the crude ethanolic extract was evaluated on carrageenan-induced paw edema in albino rats. The results of this study revealed the inhibition of oedema by the crude extract and three of its fractions at a dose of 50 mg/kg (Owolabi et al. 2020).

Several extracts prepared by maceration of the bark powder in n-Hexane, diethyl ether, ethanol and water were used to evaluate the anti-inflammatory activity of *Feretia apodanthera* Del. using the carrageenan-induced paw edema model. The anti-inflammatory effects of the four extracts at 400 mg/kg were significantly ($p > 0.05$) lower than those of ketoprofen (50 mg/kg) during the first, second and third hour. At the fourth and fifth hour, all extracts showed significantly higher anti-inflammatory potential than ketoprofen, except for the hexane extract. Of all the compounds tested, the ethanolic extract had the highest inhibition (93.35%) at the fifth hour (Owolabi et al. 2018).

Antimalaria activity

The antimalarial activity of a methanolic macerate of *Feretia apodanthera* Del. leaves was evaluated in vitro on two Plasmodium falciparum strains maintained in continuous culture; the chloroquine-sensitive D6 strain and the chloroquine-resistant W2 strain. The 50% inhibitory concentration

(IC_{50}) of *Feretia apodanthera* Del. extract was less than 25 µg/ml on the W2 strain, while that of chloroquine (positive control) was 0.055 µg/ml. A fractionation of the methanolic extract yielded nine fractions. Three of these fractions containing proanthocyanidins and iridoids showed improved antiplasmodial activity compared to the crude extract (Ancolio et al. 2002).

A synergistic effect was demonstrated between the methanolic fraction of *Feretia apodanthera* Del. leaves, tetrahydoharmane isolated from *Guiera senegalensis*, total alkaloids from *Nauclea latifolia* and ursolic acid isolated from *Mitragyna inermis*. These three plants were individually associated with *Feretia apodanthera* Del. in traditional remedies for fever and malaria. The joint action ratios were 1.8; 1.2 and 2.5 respectively (Azas et al. 2002).

In addition, an inhibitory activity (IC_{50} of 9.54 µg/ml) on the growth of chloroquine-resistant Plasmodium falciparum was found, using aqueous extracts of *Feretia apodanthera* Del. bark. Dichloromethane extracts of leaves had an IC_{50} of 6.07 µg/ml (Diallo et al. 2007).

Antiangiogenic activity

The ability of the methanolic extract of the aerial parts of *Feretia apodanthera* Del. to interfere with the recognition of vascular endothelial growth factor receptor 1 (VEGFR-1/Flt-1) by members of the vascular endothelial growth factor (VEGF) family: VEGFs/VEGFR-1 (Flt-1), was tested by competitive ELISA. The extract showed good inhibitory activity on VEGFs/Flt-1 interaction at a concentration of 100 mg/L (Pesca et al. 2013).

Antibacterial activity

The antibacterial activity of an aqueous decoctate and a hyro-acetone maceration of the aerial parts (bark and leaves) of *Feretia apodanthera* Del. was evaluated. Agar diffusion and liquid microdilution methods were used. The hydro-acetone extracts were then fractionated by column chromatography and the antibacterial activity was tested by the agar diffusion method. The hydro-acetone extract at doses of 200, 400 and 600 µg showed antibacterial activity ($d \geq 8$ mm; MIC ≤ 2.5 mg/ml) against *Bacillus licheniformis*, *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa* and *Staphyloccocus aureus*. The aqueous extract at the same doses was only active against *Escherichia coli*, *Bacillus licheniformis* and *Staphyloccocus aureus*. However, the fractions at the dose of 20 µg were selectively more active on *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, with significant activity on *Pseudomonas* ($d \geq 11$ mm) compared to the two standards chloramphenicol (no inhibition) and tetracycline ($d = 16$ mm) (Coulibaly et al., 2019).

The aqueous extract and alkaloid fraction of *Feretia apodanthera* Del. stem barks were tested for antibacterial activity by the well diffusion and broth microdilution methods. With the diffusion method, the aqueous extracts and the alkaloid-rich fraction were active against *Staphylococcus aureus*, *Escherichia coli*, *Proteus vulgaris*, *Providencia stuartii* and *Pseudomonas aeruginosa*. The diameters of the zone of inhibition (DZI) ranged from 5.1 to 17.8 mm. The extracts and fraction had high activity against *Staphylococcus aureus*, the DZIs were 17.1 and 17.8 mm respectively. The aqueous extract and the alkaloid fraction also gave significant activities by the broth microdilution method. The alkaloid fraction had the same minimum inhibitory concentration (MIC) of 6 mg/ml for all five strains tested. With the aqueous extract, the MIC was 12 mg/ml for *Staphylococcus aureus*, 6 mg/ml for *Escherichia coli*, 6 mg/ml for *Proteus vulgaris*, 3 mg/ml for *Providencia stuartii* and 12 mg/ml for *Pseudomonas aeruginosa* (Njimoh et al. 2018).

Anti-diabetic activity

The inhibitory activity of aqueous decoctate and hydro-acetone macerate of bark and leaves of *Feretia apodanthera* Del. was tested on α-amylase and α-glucosidase. Only the hydro-acetone extract showed significant inhibition of α-amylase ($21.60 \pm 1.69\%$). The inhibition of α-glucosidase was tested at different concentrations (25 µg/ml, 50 µg/ml, 100 µg/ml). Significant inhibitory activity was presented at all three concentrations ($96.51 \pm 0.14\%$; $96.70 \pm 0.27\%$ and $98.01 \pm 0.49\%$) only with the hydroacetone extract. Further fractionation of the hydro-acetone extract yielded nine (9) fractions, which were examined for anti-hyperglycemic activity. However, all fractions showed low inhibition of α-amylase activity, with the exception of fractions F2 ($33.15 \pm 3.18\%$) and F1 ($57.24 \pm 0.99\%$) (Coulibaly et al. 2020).

Cytotoxicity

The effect of a methanolic macerate of *Feretia apodanthera* Del. leaves and three of its fractions was studied on the viability and proliferation of THP1 cells (human monocytes). The concentration of extracts inducing a 50% decrease in cell growth (IC_{50}) and cell viability (LC_{50}) compared to a control culture was assessed by flow cytometry. The crude extracts had an LC_{50} greater than 25 µg/ml. The fractions showed LC_{50} values in the range of 200 and 400 µg/ml (Ancolio et al. 2002).

The ability of an aqueous extract and an alkaloid fraction of the stem bark of *Feretia apodanthera* Del. to induce cytotoxicity was studied using 3T3 cell lines and a standard MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) bioassay. After two days of culture, cells were

incubated for 24 h at 37 °C with different concentrations of the aqueous extract (1, 20, 40, 80, 100 µM) and the alkaloid fraction (1, 20, 40, 80, 100 µM). Doxorubucine (3 µM) was used as a positive control. Incubation of these cell lines with different concentrations of the aqueous extracts and the alkaloid fraction up to a concentration of 20 µM and 5 µM, respectively, for 24 h produced no cell toxicity. However, incubation of 3T3 cells with higher concentrations of the test substances (> 40 µM) produced greater cell death with IC_{50} of 39.41 ± 0.95 µM and 38.45 ± 1.64 µM, respectively, for the aqueous extract and alkaloid fraction (Njimoh et al. 2018).

Toxicity

The possible toxicological effects of ethanolic extracts of *Feretia apodanthera* Del. root bark were evaluated. The results of this study showed no mortality following administration of the extracts, even at doses up to 5000 mg/kg in albino rats. The median lethal dose (LD_{50}) of ethanolic extracts of *Feretia apodanthera* Del. root bark was therefore estimated to be greater than 5000 mg/kg (Owolabi et al. 2020).

The acute toxicity evaluation of an aqueous extract and an alkaloid fraction of the stem bark of *Feretia apodanthera* Del. was performed in female albino rats. Neither the aqueous extract nor the alkaloid fraction had any effect on behaviour and weight. No mortality was reported following administration of extracts and the 5000 mg/kg fraction (Njimoh et al. 2018).

In male and female mice, the acute toxicity of a fraction of iridoid glycosides isolated from the stem bark of *Feretia apodanthera* Del. was studied. At doses ranging from 720 mg/kg to 5760 mg/kg, the fractions appeared to be lethal and caused the death of the animals within 24 to 48 h. Mice that died following administration of a high dose (2880–5760 mg/kg) of extracts showed signs of respiratory failure (decreased respiratory rate and irregular breathing), panting and coma before death. The internal organs, however, showed no unusual signs and were found to be normal in size and colour compared to the control. The median lethal dose (LD_{50}) of the fraction was 2197.7 mg/kg (Taiwe et al. 2016).

Conclusion

The present review is based on the collection and analysis of data on the traditional medicinal applications of *Feretia apodanthera* Del. as well as on phytochemical, pharmacological and toxicological aspects.

So far, phytochemical research has not established a significant correlation between the chemical constituents of the plant and their pharmacological effects. Only an anticonvulsant effect has been attributed to the iridoid glycosides isolated from the stem bark of *Feretia apodanthera* Del.

The safety profile of *Feretia apodanthera* Del. is not clearly established. Indeed, the toxicological studies carried out are partial. Toxicological investigations of the plant have concentrated on the stem bark and root bark, with very little attention paid to the leaves. Also, only the acute toxicity was evaluated in these studies. Therefore, it is important to study the toxicity of *Feretia apodanthera* Del. in more detail to justify its safety.

Various biological activities have been demonstrated from the extracts of *Feretia apodanthera* Del. In the epilepsy study, a potent therapeutic effect on generalised tonic–clonic seizures was found, which deserves further exploration of the mechanism of action and the molecules responsible for the activity. However, the pharmacological activities were mostly tested on totum, with little use of bio-guided isolation methods. Similarly, several pharmacological activities were simply tested in vitro, such as antioxidant activity, antimalarial activity and antidiabetic activity. Generally speaking, studies on the plant have been carried out on the bark and roots. Further trials with the leaves could be carried out to check whether the same activities observed with the barks and roots can be obtained with the leaves. Leaves have less impact on the environment and are a more abundant and available resource.

While the therapeutic effects of *Feretia apodanthera* Del. on gastrointestinal disorders including dysentery and stomach ache have been indicated in ethnomedicinal uses, there are no scientific studies supporting these uses. The same is true for the antihypertensive activity and antinociceptive effect. As pain and gastrointestinal disorders are common human ailments, further studies should explore these effects to establish a link between traditional uses and pharmacological effects. As previous research has shown the high content of secondary metabolites such as tannins and flavonoids in the plant, *Feretia apodanthera* Del. could thus be a potential source of new bioactive compounds for the treatment of gastrointestinal disorders.

Thus, the information provided in this review will help to better understand the therapeutic potential of this medicinal plant in order to prompt further studies on the synthesis of new drugs from *Feretia apodanthera* Del.

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Declarations

Ethical approval This article does not contain any studies involving animals performed by any of the authors. This article does not contain any studies involving human participants performed by any of the authors.

Conflict of interest Gnièmèfèrètien Nounaféri Awa Silué has no conflict of interest. Kampadilemba Ouoba has no conflict of interest. Francis Ngolsu has no conflict of interest. Salfo Ouedraogo has no conflict of interest. Gisèle Kouakou-Siransy has no conflict of interest. Rasmané Semdé has no conflict of interest.

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