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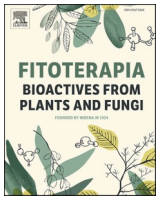

Review

Anogeissus leiocarpus (DC.) Guill. & Perr. (Combretaceae): A review of the traditional uses, phytochemistry and pharmacology of African birch

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ABSTRACT

Anogeissus leiocarpus (DC.) Guill. & Perr. belongs to the family Combretaceae and is used both by African traditional medical practitioners and livestock rearers to treat diseases such as African trypanosomiasis, animal diarrhoea, asthma, cancer, cough, diabetes, dysentery, erectile dysfunction, fever, giardiasis, helminthiases, meningitis, menstrual disorders, monkeypox, oral infections, poliomyelitis, sickle cell anaemia, snake bites, toothache, urinary schistosomiasis, and yellow fever. Some of these activities have been associated with the presence of polyphenols in the plant which include ellagic acid derivatives, flavonoids, stilbenes, tannins, and triterpenes. Several bioactive molecules have been identified from *A. leiocarpus*. These include the main active constituents, ellagitannins, ellagic acid derivates, flavonoids and triterpenes. Pharmacological studies have confirmed its antibacterial, antifungal, antihyperglycemic, antihypertensive, antimalarial, antioxidative, anti-parasitic, antitumour and anti-ulcer effects. The stem bark has been investigated mainly for biological activities and phytochemistry, and it is the most mentioned plant part highlighted by the traditional users in ethno-medicinal surveys. *In vitro* and *in vivo* models, which revealed a wide range of pharmacological actions against parasites causing helminthiasis, leishmaniasis, malaria and trypanosomiasis, have been used to study compounds from *A. leiocarpus*. Because of its uses in African traditional medicine and veterinary practices, *A. leiocarpus* has received considerable attention from researchers. The current review provides a comprehensive overview and critical appraisal of scientific reports on *A. leiocarpus,* covering its traditional uses, pharmacological activities and phytochemistry.

1. Introduction

The *Anogeissus* DC. was elevated to a genus by Guillemin et al. [1] and it comprises *Anogeissus acuminata* (Roxb. ex DC.) Guill. & Perr., *A. latifolia* (Roxb. ex DC.) Guill. & Perr., and *A. leiocarpa* (DC.) Guill. & Perr. Other species of *Anogeissus* include *A. bentii* Baker, *A. dhofarica* A. J. Scott, *A. pendula* Edgew., *A. rivularis* (Gagnep.) O. Lecompte, and *A, sericea* Brandis [2]. *Anogeissus leiocarpus* (DC.) Guill. & Perr. (Synonym, *A. schimperi* Hochst. Ex. Hutch & Dalziel), also known as African birch, is a deciduous tree in the family Combretaceae. This family has about 20 genera and 600 species. The genus *Anogeissus* has eight species, and only *A. leiocarpus* (Fig. 1) is native to tropical Africa. Five are found in tropical Asia while two are found in Arabia [3,4].

A. leiocarpus is an important tree in the cultures of the Malians and Burkinabé. It is an excellent source of valuable timber, and its wood produces good charcoal. Malians and Burkinabé have a traditional history of using dyes from this plant in Bogolan textile techniques. It is widely grown for its ornamental and religious purposes in Burkina Faso

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Fig. 1. Image of the bark of *A. leiocarpus* (DC.) Guill. & Perr. The plant grows inside the University of Ibadan Botanical Gardens (Photo taken in March 2021). Note: The specie name, *Anogeissus leiocarpus* (DC.) Guill. & Perr., has been checked with World Flora Online [150].

[5]. *A. leiocarpus* root is widely used by the people of southwestern Nigeria as a chewing stick and it is widely distributed in northern Nigeria [6]. This plant has various medicinal purposes among traditional healers in Africa, and it is used for veterinary purposes [3]. Arbab [7] published a short review of *A. leiocarpus*, however, a lot more pharmacological and phytochemical reports are now available on this plant. Therefore, this review provides a comprehensive report and critical appraisal of recent pharmacological and phytochemical data published on *A. leiocarpus*.

2. Taxonomy [2,8]

Order: Myrtales
Family: Combretaceae
Genus: *Anogeissus*
Specie: *Anogeissus leiocarpus* (DC.) Guill. & Perr.
Synonyms: *Anogeissus leiocarpa* f. *grandifolia* Engl. & Diels
Anogeissus leiocarpa f. *parvifolia* Hochst. ex Engl. & Diels.
Anogeissus leiocarpa var. *schimperi* (Hochst. ex Hutch. & Dalziel) Aubrev.
Anogeissus leiocarpus var. *schimperi* (Hochst. ex Hutch. & Dalziel) Aubrev.
Anogeissus schimperi Hochst. ex Hutch. & Dalziel.
Conocarpus leiocarpus DC.
Conocarpus schimperi Hochst. ex A. Rich.
Terminalia leiocarpa (DC.) Baill.

3. Botanical description and ethnomedicine

A. leiocarpus has a height of 15 to 18 m with a diameter of 1 m [9]. It is native to the savannas and tropical Africa. Some of the West African countries where the *A. leiocarpus* plant grows include Benin Republic, Cameroon, Côte d'Ivoire, Gambia, Ghana, Guinea, Mali, Niger, Nigeria, Senegal, and Togo. It also grows in Ethiopia, Sudan, and some other East African countries [5]. This plant often has drooping branches and grey stem bark which turns to dark grey with age. Opposite-leaved or subalternate, ovate to elliptic, or ovate-lanceolate. The leaves of the young plants are silky and glossy with short hairs appressed above, but those of the mature plants are sparsely silky to sparsely tomentose. Inflorescences are axillary and terminal, and flower heads are 8–15 mm in diameter. Flowers are yellow and calyx stalks are 3–4 mm long. Filaments and style are 3 mm long. Fruits are about 4–7 mm long and 6–9 mm broad [2].

Several diseases are treated in northern Nigeria with this plant. Structured questionnaires were administered to farmers, herb traders, traditional healers, and civil servants in Kaduna State to capture the plants they use to treat impotence among men. This study identified that the indigenous population used the leaf of *A. leiocarpus* and stem of *Detarium senegalense* J. F.Gmel (Caesalpiniaceae), taken directly with soft drinks or food, to treat erectile dysfunction [10]. The plant's stem bark is used to manage some symptoms of COVID-19 (Cough, Fever, body pains) in Cameroon [11]. People in Abeokuta, south-western Nigeria use *A. leiocarpus* in the treatment of amenorrhoea, dysmenorrhoea, menorrhagia, oligomenorrhoea and after-childbirth problems that are commonly reported in maternity homes in that area [12]. Leaf, stem, and root barks are also being employed in Nigeria's Sokoto State as macerate or powder to treat breast, head, neck, and skin cancer [13].

Structured questionnaires and direct interviews of traditional snake bite healers, Fulani cattle rearers and farmers in six communities in Sokoto (northern Nigeria) reported *A. leiocarpus* (vernacular: Marke) as a potent plant in treating snake poisons [14]. Thirty traditional healers in Algoz (South Kordofan), Sudan were surveyed with semi-structured questionnaires about the use of plants in the area. Local users reported the stem bark of *A. leiocarpus* as an effective treatment for toothaches [15]. An earlier study by Musa et al. [16] in Blue Nile State, southeastern Sudan identified oral decoction of the stem bark in managing cough, dysentery, and giardiasis. Another ethnobotanical survey conducted between 2012 and 2013 in the northern Kordofan of Sudan used semi-structured interviews to collect information from 258 local users of medicinal plants. The study identified *A. leiocarpus* for managing diabetes, dysentery, and malaria among the locals in that area [17].

A. leiocarpus is important in tropical veterinary medicine to treat parasitic infections caused by helminths such as nematodes [18]. Helminth elimination improves livestock production throughout the tropics, and anthelminthic plants are effective ways of parasite control in animals [19]. Fulani herdsmen in Nigeria recognise helminths as a great threat to the lives of calves under one year old, and this often prompts them to start a routine anthelmintic treatment with herbal formulations within the first week of birth [20]. Hammond et al. [19] noted that both developed and developing countries use anthelmintic plants on their animals. For example, *Chenopodium* oil was included in the British Veterinary Codex (1953, 1965) to treat *Toxascaris* and *Toxocara* infections in dogs, *Ascariasis* in horses and pigs, and *Strongylus* diseases in horses before the advent of synthetic anthelmintic molecules. In Africa, an herbal mixture containing *A. leiocarpus* stem bark, *Securinega virosa* (Roxb. ex Willd.) Baill. leaf and stems, *Khaya senegalensis* (Desr.) A. Juss. stem bark, and *Nauclea latifolia* Smith root was considered one of the most effective veterinary anthelmintic recipes [19]. An ethnobotanical and ethnopharmacological survey conducted in Northern Côte d'Ivoire revealed that *A. leiocarpus* could be used for various veterinary purposes such as intestinal worm infections, gastrointestinal disorders, and bites. Milled *A. leiocarpus* fruits are added to the bran of *Pennisetum glaucum* L. or *Sorghum bicolor* (Linn) Moench with salt. Cattle, goats, or sheep are fed then on it. Alternatively, some water is added to the powdered leaf, filtered, and orally ingested by animals, and then applied topically on affected wound parts once a day for 3 days [21].

It has been extensively reported that *A. leiocarpus* is effective in treating parasitic infections such as urinary schistosomiasis [22], and African animal trypanosomiasis [23]. Offiah et al. [24] interviewed farmers in ten local governments of Plateau State, Nigeria between October, and December 2010. Farmers in these high cattle-populated areas reported *A. leiocarpus* is used to treat diarrhoea in animals. The stem bark of *A. leiocarpus* has been identified in malaria treatment in Ghana's Wechiau Community Hippopotamus Sanctuary area [25] and northern Nigeria [26]. The ethnomedicinal information on *A. leiocarpus* is summarised in Table 1.

4. Phytochemistry

There are many phenolic compounds found in the genus *Anogeissus*, including flavonoids and tannins. Phytochemical investigations of extracts of *A. leiocarpus* have revealed phytochemicals such as alkaloids, flavonoids, saponins, steroids, tannins, and triterpenes [37].

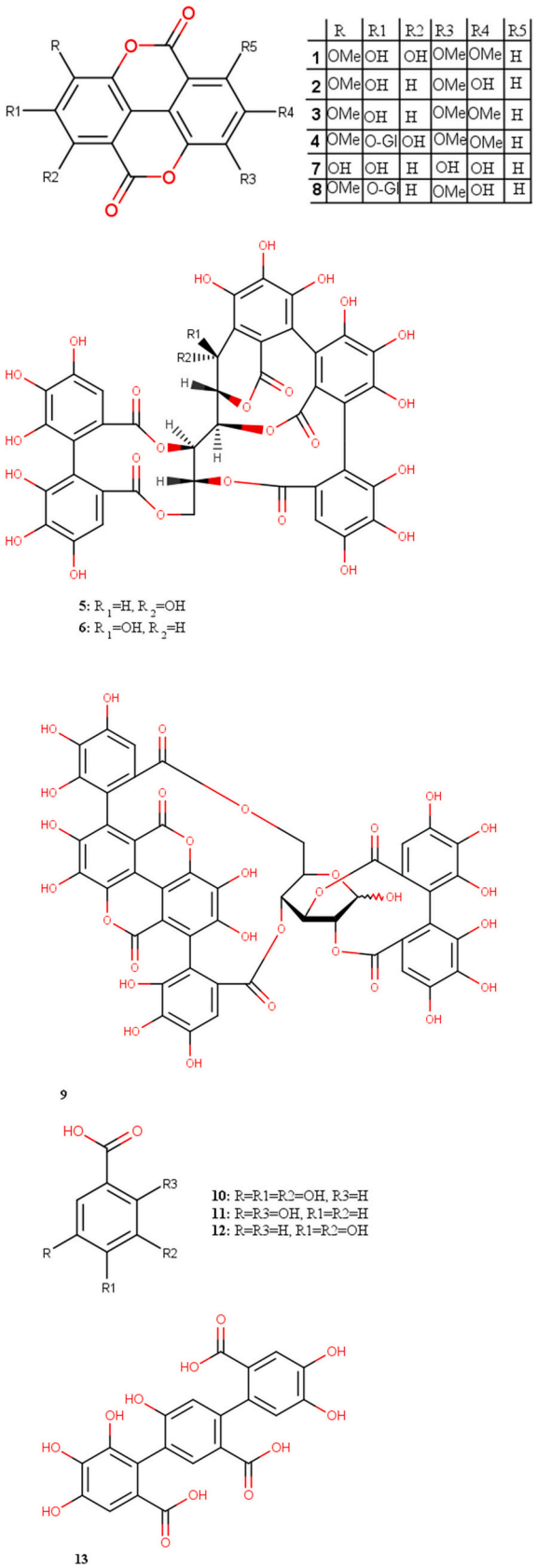
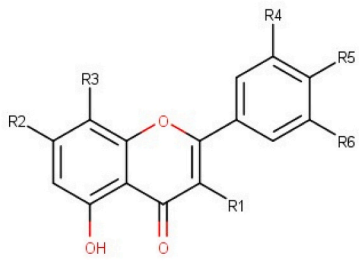
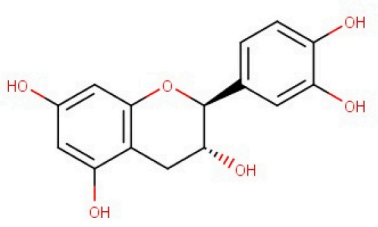


Fig. 1. Structures of some compounds from *A. leiocarpus*.



	R1	R2	R3	R4	R5	R6
15	OH	OH	OH	OH	OH	H
16	O-Gl-Rha	OH	H	OH	OH	H
17	H	O-Rha	H	H	OMe	OH
18	O-Gl	OH	H	OH	OH	H
19	H	OH	O-Rha	H	OH	H
20	OH	OH	H	H	OH	H
27	O-Gl	OH	H	H	OH	OH
28	O-GA	OH	H	H	OH	OH



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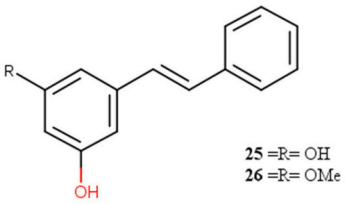
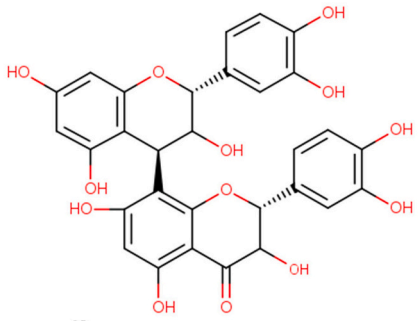


25 =R= OH
26 =R= OMe



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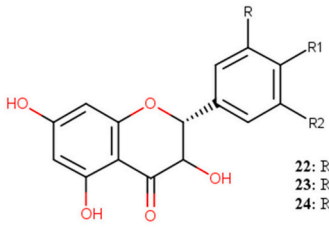
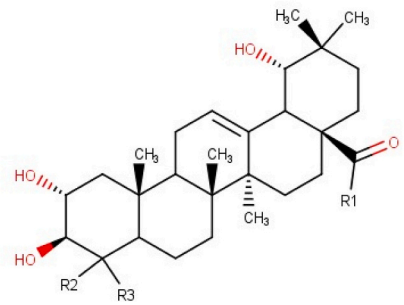


22: R=R1=R2=OH
23: R=R2=H, R1=OH
24: R=H, R1=R2=OH



	R1	R2	R3
29	O-Gl	CH_2OH	CH_2OH
30	O-Gl	CH_2OH	Me
31	O-Gl	Me	CH_2OH
32	OH	Me	CH_2OH
33	OH	CH_2OH	CH_2OH
34	OH	CH_2OH	Me

Fig. 1. (*continued*).

4.1. Tannins and ellagic acid derivatives

Compound 3,4′,3′-tri-*O*-methylflavellagic acid **(1)** was first isolated from a natural source from *A. schimperi* (syn: *A. leiocarpus*) [38]. Its occurrence was with 3,3′-di-*O*-methylellagic acid **(2)** (which crystallized as yellow flakes from the aqueous acetone fraction) and tri-*O*-methylellagic acid **(3)**. About a decade later, 3,4′,3′-tri-*O*-methylflavellagic acid **(1)**, together with its glycoside, 3,4′,3′-tri-*O*-methylflavellagic acid 4-*O*-

Table 1
Traditional uses of *A. leiocarpus*.

Country	Local name	Plant part	Indication	Preparation	References
Northern Nigeria	Marke (H), Kojoli (F)	Stem bark Root, stem, leaf	Viral infections such as monkeypox, poliomyelitis COVID-19, meningitis, poliomyelitis, yellow fever	Concoction/boil with red potash. Administered orally. Oral decoction. Boil/add red potash. 2–3 cupfuls to be administered thrice a day	[27]
		Leaf	Erectile dysfunction	Mill with the bark of *D. senegalense* and take with a soft drink/meal daily.	[10]
		Leaf, bark and root	Breast, head, neck and skin cancer	Maceration or powder	[13]
		Stem bark	Fever/malaria		[26,28]
North central, Nigeria (Idoma tribe)	Otla/Ofiotra (I)	Root	Tuberculosis	Boil the root material in water for drinking	[29]
Idoma		Leaves and stem bark	Typhoid fever	Leaves of *A. leiocarpus* and *Annona senegalensis* Pers. are sun-dried for 40 min. Put in water to make a decoction. Take about 1 cup twice daily for 3 weeks. Bark boiled in clean water for 30 min. About 300 mL taken thrice a day	[30]
Southwest (Ogun, Osun, Oyo), Nigeria	Ayin (Y)	Stem bark	Asthma	1. Recipes: *Bridelia ferruginea* Benth., *A. leiocarpus, Anacardium occidentale* L. The plant materials are cut in pieces and boiled. An adult takes a small tumbler full three times a day while a child takes a teaspoon-full three times a day. 2. Recipes: *Zingiber officinale* Roscoe, *A. occidentale, B. ferryginea, Allium ascalonicum* L., *Terminalia glaucescens* Planch. ex Benth., *A. leiocarpus.* Plant materials are boiled for about half an hour with water. An adult takes a tumbler morning and night while a child takes a teaspoon.	[31]
Ghana	Hehe	Leaf, stem	Diabetes mellitus	Decoction	[32]
Nigeria		Stem bark	Human and animal helminthiases	Stem bark of *A. leiocarpus,* and *S. virosa* (leaf & stems), *K. senegalensis* (stem bark), and *N. latifolia* (root)	[19,20]
Southwestern Nigeria			Haemorrhoids, sickle cell diseases, oral infections,		[6]
Southwestern Nigeria		Root	Malaria	Decoction	[33]
Nigeria		Stem bark	Diabetes	Decoction	[34]
Northwestern Nigeria		Stem bark	Snakebite	Oral decoction and topical	[14]
Algoz (southern Kordofan), Sudan	Sahab	Stem bark	Toothache	Tooth cavity filled with plant powder	[15]
Blue Nile State, Sudan	Sahab	Stem bark	cough, dysentery, and giardiasis	Decoction	[16,35]
Northern Kordofan, Sudan	Sahab	Inflorescence	diabetes, dysentery, and malaria	Maceration	[17]
Abeokuta, Nigeria		Stem bark	Menstrual disorders and after-childbirth problems	Decoction	[12]
Northern Côte d'Ivoire	Guenmin, N'galama	Fruits, leaf	Intestinal worms, gastrointestinal disorders and bites in animals, malaria	1. Milled the fruit of *A. leiocarpus* plus the bran of *Pennisetum glaucum* L. or *S. bicolor* and salt, then fed to the animals. 2. Powdered dry leaf added to water, then filtered, ingested to animals orally, and applied topically on the affected wound area, one time a day for 3 days	[21,153]
Burkina Faso	Siiga (M)	Leaf	African animal trypanosomiasis	Mill the leaves. Add clean water and sift. Give to animals once daily	[23]
Niono District, Mali	Ngalama (B)	Leaf	Urinary schistosomiasis	A decoction of *A. leiocarpus* fresh or dry leaves is taken once a day for 8 days.	[22]
Plateau State, Nigeria		Leaf, stem bark, seeds	Animal diarrhoea	Ingested orally	[24]
Togo		Leaf	Liver diseases	Decoction, infusion	[36]

B=Bambara; F=Fulani; I=Idoma; H=Hausa; M = Mooré; Y=Yoruba.

glucoside **(4)**, was isolated again from the plant's stem [39]. Also, Chaabi et al. [40] isolated 3,3′,4′-tri-*O*-methylflavellagic acid **(1)**, 3,3′-di-*O*-methylellagic acid **(2)** and 3,4′,3′-tri-*O*-methylflavellagic acid-4′-*β*-D-glucoside **(4)** from *A. leiocarpus*. An acetylated ellagic acid derivative, di-*O*-methyl ellagic acid, and its xylose saponin have been tentatively characterised from the root of *A. leiocarpus* through HPLC-DAD and UHPLC/QTOF-MS analyses [41].

An HPLC coupled with MS and ^{1}H NMR techniques were used for phytochemical profiling of the aqueous ethanolic extract of the stem bark of *A. leiocarpus*. The study identified 43 ellagitannins and ellagic acid derivatives [42] (Table 2). Some of the compounds reported include acutissimin, castalagin **(5)**, castalagin isomer, castalin, casuarictin/potentillin, di-methyl-ellagic acid pentoside isomer, dehydrated tergallic acid c-glucoside isomer, 3,3′-*O*-dimethyl ellagic acid 4-*O*-*β*-glucopyranoside **(8)**, ellagic acid **(7)**, ellagic acid hexoside, ellagic acid-dihexoside, eucaglobulin, *β*-1-*O*-ethylvescalagin, gallic acid **(10),** guajavin B or eugenigrandinin A, hexahydroxydiphenoyl (HHDP) glucose, punicalagin **(9)**, pedunculagin, punicalagin isomer, quinic acid, roburin A/D, roburin B, roburin E, roburin E isomer, tellimagrandin I or galloyl-HHDP-glucose, 3,3′,4-tri-*O*-methylflavellagic acid **(1)**, 3,3′,4-tri-*O*- methyl-*β*-1-*O*-ethylvescalagin, vescalagin **(6),** vescalin. Salih et al. [43] identified dimethyl-ellagic acid, dimethylellagic acid glucopyranoside, dimethylellagic acid xylopyranoside, digalloyl-β-D-glucose, ellagic acid derivatives, dimethyl ellagic acid glucoside, pentagalloyl-glucose, dimethyl ellagic acid, an acetylated ellagic acid derivative, and phenolic acids such as protocatechuic acid **(12)** and gallic acid **(10)** in the antibacterial methanol root extracts. Castalagin **(5)**, ellagic acid **(7)**, flavogallonic acid **(13)**, punicalagin **(9)** and terchebulin were reported in the Sephadex LH-20 chromatographed *n*-butanol extract of the stem bark [44]. HPLC and LC-ion trap-top of flight-mass spectrometry (LC-IT-TOF-MS) analysis of the aqueous leaf extract led to the identification of punicalagin isomers (*α* & *β*) and its galloyl ester, 1-*O*-galloyl-punicalagin

Table 2
Compounds identified in *A. leiocarpus*.

Compounds	Method of Isolation/ Characterization/ Identification	Plant parts	References
Tannins and ellagic acid derivatives			
Castalagin **(5)**	Sephadex LH-20/ HPLC/^{1}H and ^{13}C NMR	Stem bark	[44]
Vescalagin **(6)**	HPLC-DAD-MS & ^{1}H NMR	Stem bark	[42]
Punicalagin isomers (α & β) and its galloyl ester, 1-*O*-galloyl-punicalagin	LC-IT-TOF-MS analysis	Leaf	[45]
Ellagic acid **(7)**, gallic acid **(10)**	HPLC-DAD-MS & ^{1}H NMR	Stem bark	[42]
Flavogallonic acid **(13)**	Sephadex LH-20/ HPLC/^{1}H and ^{13}C NMR	Stem bark	[53]
Dimethyl ellagic acid **(2)**	HPLC-DAD & UHPLC/QTOF-MS	Root	[41]
Acetylated ellagic acid derivative	HPLC-DAD & UHPLC/QTOF-MS	Root	[41]
Di-methyl-ellagic acid xyloside	HPLC-DAD & UHPLC/QTOF-MS	Root	[41]
3,3′,4′-Tri-*O*-methylflavellagic acid **(1)**	Precipitated from aqueous acetone faction/IR/NMR	Stem bark	[38]
Hexahydroxydiphenoylhexose	HPLC and LC-ion trap-top of flight-mass spectrometry (LC-IT-TOF-MS)	Leaf	[46]
3,3′,4′-Tri-*O*-methylflavellagic acid 4-*O*-glucoside **(4)**	LC-IT-TOF-MS	Leaf	[46]
Di-*O*-methylflavellagic acid	LC-IT-TOF-MS	Leaf	[46]
Di-*O*-methylflavellagic acid isomer	LC-IT-TOF-MS	Leaf	[46]
3,3'-Di-*O*-methylellagic acid 4-*O*-glucoside **(8)**	LC-IT-TOF-MS	Leaf	[46]
Di-*O*-methylellagic acid-*O*-deoxyhexoside	LC-IT-TOF-MS	Leaf	[46]
Galloylquinic acid isomer	LC-IT-TOF-MS	Leaf	[46]
Di-*O*-methylcoruleoellagic acid	LC-IT-TOF-MS	Leaf	[46]
Galloylhexose isomer, galloylquinic acid isomer, digalloylhexose	LC-IT-TOF-MS	Leaf	[46]
Punicacortein C or D	LC-IT-TOF-MS	Leaf	[46]
3-*O*-Methylellagic acid	LC-IT-TOF-MS	Leaf	[46]
Ellagic acid *O*-glucuronide	LC-IT-TOF-MS	Leaf	[46]
Chebulagic acid	LC-IT-TOF-MS	Leaf	[46]
Ellagic acid *O*-hexoside isomer	LC-IT-TOF-MS	Leaf	[46]
4-methoxycinnamic acid	LC-IT-TOF-MS	Leaf	[46]
Cornusiin B or isomer	LC-IT-TOF-MS	Leaf	[46]
Corilagin or isomer	LC-IT-TOF-MS	Leaf	[46]
Tellimagrandin I or isomer	LC-IT-TOF-MS	Leaf	[46]
Casuarinin	LC-IT-TOF-MS	Leaf	[46]
Flavonoids, stilbenes and flavonoidal glycosides			
Catechin **(14)**	Silica gel column chromatography, Sephadex LH-20/ HPLC/NMR (1D and 2D)/LC-ESI-MS	Leaf	[47]
Isoquercetin **(18)**	Silica gel column chromatography, Sephadex LH-20/ HPLC/NMR (1D and 2D)/LC-ESI-MS	Leaf	[47]
Kaempferol **(20)**	Silica gel column chromatography, Sephadex LH-20/ HPLC/NMR (1D and 2D)/LC-ESI-MS	Leaf	[47]
Procyanidin B2 **(21)**	Silica gel column chromatography, Sephadex LH-20/ HPLC/NMR (1D and 2D)/LC-ESI-MS	Leaf	[47]
Quercetin **(15)**	Silica gel column chromatography, Sephadex LH-20/ HPLC/NMR (1D and 2D)/LC-ESI-MS	Leaf	[47]
Rutin **(16)**	Silica gel column chromatography, Sephadex LH-20/ HPLC/NMR (1D and 2D)/LC-ESI-MS	Leaf	[47]
Vitexin **(19)**	Silica gel column chromatography, Sephadex LH-20/ HPLC/NMR (1D and 2D)/LC-ESI-MS	Leaf	[47]
4H-1-Benzopyran-4-one, 7-[(6-deoxy-α-L-mannopyranosyl) oxy]-5-hydroxy-2-(4-hydroxy-3-methoxyphenyl) **(17)**	Silica gel column chromatography, Sephadex LH-20/ HPLC/NMR (1D and 2D)/LC-ESI-MS	Leaf	[47]
Ampelopsin **(22)**	HPLC-DAD and UHPLC/Q-TOF MS	Root	[43]
Aromadendrin **(23)**	HPLC-DAD and UHPLC/Q-TOF MS	Root	[43]
Taxifolin **(24)**	HPLC-DAD and UHPLC/Q-TOF MS	Root	[43]
Pinosylvin **(25)**	HPLC-DAD and UHPLC/Q-TOF MS	Root	[43]
4′-Methylpinosylvin **(26)**	HPLC-DAD and UHPLC/Q-TOF MS	Root	[43]
Methyltaxifolin	HPLC-DAD and UHPLC/Q-TOF MS	Root	[43]
Quercetin 3-*O*-rhamnoside **(27)**	HPLC coupled with MS	Leaf	[48]
Quercetin 3-*O*-glucuronide **(28)**	HPLC coupled with MS	Leaf	[48]
Kaempferol 3-*O*-hexoside	HPLC coupled with MS	Leaf	[48]
Quercetin rhamnoglucosyl	Open glass column chromatography/ UV/IR/1D-NMR	Leaf	[49]
Isoflavonoid glucoside	Open glass column chromatography/ UV/IR/1D-NMR	Leaf	[49]
Gallocatechin	HPLC-ESI-MS	Stem bark	[46]
Procyanidin B isomer	HPLC-ESI-MS	Stem bark	[46]
Epigallocatechin	HPLC-ESI-MS	Stem bark	[46]
Epigallocatechin-3-*O*-gallate	HPLC-ESI-MS	Stem bark	[46]
Epicatechin	HPLC-ESI-MS	Stem bark	[46]
Mangiferin	HPLC-ESI-MS	Stem bark	[46]
Myricetin-*O*-hexoside	HPLC-ESI-MS	Stem bark	[46]
Quercetin-*O*-galloylhexoside	HPLC-ESI-MS	Stem bark	[46]
Isoquercitrin	HPLC-ESI-MS	Stem bark	[46]
Luteolin 7-*O*-glucoside	HPLC-ESI-MS	Stem bark	[46]
Avicularin	HPLC-ESI-MS	Stem bark	[46]
Dihydroxy-trimethoxy(*iso*) flavone	HPLC-ESI-MS	Stem bark	[46]
Pinocembrin (5,7-dihydroxyflavanone)	HPLC-ESI-MS	Stem bark	[46]
Isorhamnetin 3-*O*-glucoside	HPLC-ESI-MS	Stem bark	[46]

(*continued on next page*)

Table 2 (*continued*)

Compounds	Method of Isolation/ Characterization/ Identification	Plant parts	References
Luteolin (3′,4′,5,7-tetrahydroxyflavone)	HPLC-ESI-MS	Stem bark	[46]
isorhamnetin-*O*-glucuronide	HPLC-ESI-MS	Stem bark	[46]
Naringenin	HPLC-ESI-MS	Stem bark	[46]
Reinutrin (quercetin 3-*O*-xyloside)	HPLC-ESI-MS	Stem bark	[46]
Quercitrin (quercetin 3-*O*-rhamnoside) **(27)**	HPLC-ESI-MS	Stem bark	[46]
Triterpenes and saponins			
Trachelosperoside E1 **(29)**	Sephadex LH-20, preparative TLC/ 1D- and 2D-NMR	Stem bark	[50]
Arjunglucoside I **(30)**	Sephadex LH-20, preparative TLC/ 1D- and 2D-NMR	Stem bark	[50]
Sericoside **(31)**	Sephadex LH-20/ Prep-HPLC/UV/ ^{1}H NMR and ^{13}C NMR	Stem bark	[40]
Sericic acid **(32)**	Sephadex LH-20/ Prep-HPLC/UV/ ^{1}H NMR and ^{13}C NMR	Stem bark	[40]
Trachelosperogenin E **(33)**	Sephadex LH-20/ Prep-HPLC/UV/ ^{1}H NMR and ^{13}C NMR	Stem bark	[40]
Arjungenin **(34)**	Sephadex LH-20/ Prep-HPLC/UV/ ^{1}H NMR and ^{13}C NMR	Stem bark	[40]
Hydroxylated-trachelosperogenin hexoside	HPLC-DAD-MS and ^{1}H NMR	Stem bark	[42]
Trachelosperogenin hexoside	HPLC-DAD-MS and ^{1}H NMR	Stem bark	[42]
Arjungenin or sericic acid glycoside.	HPLC-DAD-MS and ^{1}H NMR	Stem bark	[42]
Fatty acids and other compounds			
Palmitic acid (*n*-hexadecanoic acid)	GC–MS	Leaf, root	[51]
Palmitic acid methyl ester	GC–MS	Leaf	[51]
Stearic acid (octadecanoic acid)	GC–MS	Leaf	[51]
Oleic acid (9-octadecenoic acid)	GC–MS	Leaf	[51]
Oleic acid methyl ester	GC–MS	Leaf	[51]
Z-9-Octadecenoic acid	GC and GC–MS	Leaf, stem, root	[52]
Methyltetracosanoate	GC and GC–MS	Leaf	[52]
Nopol	GC and GC–MS	Leaf	[52]
Methyl-7*E*-7-octadecenoate	GC and GC–MS	Leaf, root	[52]
Methylhexadecanoate	GC and GC–MS	Leaf, stem, root	[52]
Dodecane	GC and GC–MS	Leaf	[52]
Z,Z-9,12-octa decadienoic acid	GC and GC–MS	Leaf	[52]
Di-*n*-octylphthalate	GC and GC–MS	Leaf	[52]
Tridecane	GC and GC–MS	Leaf, root	[52]
n-Nonadecane	GC and GC–MS	Stem bark	[52]
n-Hexadecanoic acid	GC and GC–MS	Stem bark	[52]
Eicosane	GC and GC–MS	Stem bark	[52]
Docosane	GC and GC–MS	Stem bark	[52]
Tricosane	GC and GC–MS	Stem bark	[52]
Tetracosane	GC and GC–MS	Stem bark	[52]
3,7-Dimethylnonane	GC and GC–MS	Stem bark	[52]
DL-arabinose	GC and GC–MS	Stem bark	[52]
Heneicosane	GC and GC–MS	Stem bark	[52]
3*E*-3-icosene	GC and GC–MS	Stem bark	[52]
Methyl-9*Z* octadecenoate	GC and GC–MS	Stem bark	[52]
Methyl linoleate	GC and GC–MS	Root	[52]
1-(4-cycloocten-1-yl) ethenone	GC and GC–MS	Root	[52]
n-Undecanoic acid	GC and GC–MS	Root	[52]
n-Pentadecane	GC and GC–MS	Root	[52]
n-Pentadecanoic acid	GC and GC–MS	Root	[52]
1,14-tetradecanediol	GC and GC–MS	Root	[52]
Dodecanedioic acid	HPLC-ESI-MS	Leaf	[46]
Undecanedioic acid	HPLC-ESI-MS	Leaf	[46]
Hexadecanedioic acid	HPLC-ESI-MS	Leaf	[46]
3-hydroxybenzaldehyde	HPLC-ESI-MS	Leaf	[46]
Kynurenic acid	HPLC-ESI-MS	Leaf	[46]
Coumaroylshikimic acid,	HPLC-ESI-MS	Leaf	[46]
Coumaroylquinic acid	HPLC-ESI-MS	Leaf	[46]
Caffeoylshikimic acid	HPLC-ESI-MS	Leaf	[46]

[45]. In a comparison of methanol, ethyl acetate, and water-extracted *A. leiocarpus* leaves and stem bark, HPLC-ESI-MS was used to analyze phytochemicals. All the extracts contained gallic acid **(10)**, quinic acid, shikimic acid, and protocatechuic acid. Caffeic acid, chlorogenic acid, dodecanedioic acid, and ferulic acid were found in the leaf extract. Table 2 contains other compounds tentatively detected [46].

4.2. Flavonoids and stilbenes

The antiplasmodial and antileishmanial extract of *A. leiocarpus* leaves afforded eight flavonoids: catechin **(14)**, 4H-1-benzopyran-4-one, 7-[(6-deoxy-α-L-mannopyranosyl)oxy]-5-hydroxy-2-(4-hydroxy-3-methoxyphenyl) **(17)**, isoquercetin **(18)**, kaempferol **(20)**, procyanidin B2 **(21)**, quercetin **(15)**, rutin **(16)** and vitexin **(19)** [47]. The root bark extracted with methanol contained five flavonoids: ampelopsin **(22)**, aromadendrin **(23)**, methyltaxifolin, taxifolin **(24)**, and two stilbenes: 4′-methylpinosylvin **(26)** and pinosylvin **(25)** [43]. Kaempferol 3-*O*-hexoside, quercetin 3-*O*-rhamnoside **(27)**, quercetin 3-*O*-glucuronide **(28)** and were identified from the textile dye extract from *A. leiocarpus* leaves [48]. *n*-Butanol leaf extract yielded two flavonoid glycosides: quercetin rhamnoglucosyl and an isoflavonoid glucoside through successive solvent partitioning, followed by some chromatographic techniques [49].

Orlando et al. [46] identified the following compounds in their comparative phytochemical profiling of extracts from leaves and stem of *A. leiocarpus* by HPLC-ESI-MS analysis: ampelopsin or dihydromyricetin **(22)**, aromadendrin or dihydrokaempferol **(23)**, avicularin, catechin **(14)**, dihydroquercetin **(24)**, dihydroxy-trimethoxy(*iso*)flavone, epicatechin, epigallocatechin, epigallocatechin-3-*O*-gallate, gallocatechin, isoquercitrin (hirsutrin, quercetin 3-*O*-glucoside), isorhamnetin 3-*O*-glucoside, isorhamnetin-O-glucuronide, kaempferol or 3,4′,5,7-tetrahydroxyflavone **(20)**, luteolin 7-*O*-glucoside or cynaroside, luteolin or 3′,4′,5,7-tetrahydroxyflavone, mangiferin, naringenin, pinocembrin or 5,7-dihydroxyflavanone, procyanidin B isomer, quercitrin or quercetin 3-*O*-rhamnoside, quercetin **(15)**, quercetin *O*-galloylhexoside, quercetin 3-*O*-glucuronide **(28)**, reinutrin or quercetin 3-*O*-xyloside, rutin or quercetin 3-*O*-rutinoside **(16)**, taxifolin or myricetin *O*-hexoside, and vitexin or apigenin 8-C-glucoside **(19)**.

4.3. Triterpenes and saponins

Sephadex LH-20 and preparative thin layer chromatographed-extract of *A. leiocarpus* stem bark led to the isolation of two oleanane-type triterpene saponins: olean-12-en-28-oic acid 2*α*,3*β*,19*α*,23,24-pentahydroxy-β-D-glucopyranosyl ester or trachelosperoside E1 **(29)** and olean-12-en-28-oic acid 2*α*,3*β*,19*α*,23-tetrahydroxy-*β*-D-glucopyranosyl ester or arjunglucoside I **(30)** [50]. Chaabi et al. [40] reported further triterpenes and their saponins from the stem bark, including arjungenin **(34),** sericic acid **(32)**, sericoside **(31)**, trachelosperogenin E **(33)**, and trachelosperoside E1 **(29)**. Akande et al. [42] evaluated the hydroethanolic extracts of the stem bark and 16 oleanane-type triterpenoids were identified which included arjungenin **(34)**, arjungenin or sericic acid glycoside, hydroxylated-trachelosperogenin hexoside, sericoside **(31)**, trachelosperogenin, trachelosperoside E1 **(29)**, trachelosperogenin hexoside.

4.4. Others

The GC–MS analysis of the *n*-butanol leaf extract of *A. leiocarpus* identified fatty acids such as oleic acid (9-octadecenoic acid), oleic acid methyl ester, palmitic acid (*n*-hexadecanoic acid), palmitic acid methyl ester, and stearic acid (octadecanoic acid) [51]. GC and GC–MS analyses of essential oils obtained by hydro-distillation using Clevenger-type apparatus from the leaf revealed the presence of eleven compounds: dodecane, di-*n*-octylphthalate, *n*-hexadecanoic acid, methyl-7*E*-7-octadecenoate, methylhexadecanoate, methyltetracosanoate, nopol, *n*-octadecanoic acid, *Z*-9-octadecenoic acid, *Z,Z*-9,12-octadecadienoic acid, tridecane; compounds found in the essential oil extracted from the stem bark are: DL-arabinose, 3,7-dimethylnonane, docosane, eicosane, 3*E*-3-icosene, heneicosane, *n*-hexadecanoic acid, methyl-9*Z* octadecenoate, methylhexadecanoate, *n*-nonadecane, *Z*-9-octadecenoic acid, tetracosane, and tricosane; and the root oil showed fourteen compounds: bornyl angelate, 1-(4-cycloocten-1-yl) ethenone, di-*n*-octyl phthalate, *n*-docosane, *n*-hexadecanoic acid, methylhexadecanoate, methyl linoleate, methyl-7*E*-7-octadecenoate, *Z*-9-octadecenoic acid, *n*-pentadecane, *n*-pentadecanoic acid, 1,14-tetradecanediol, *n*-tridecane, and *n*-undecanoic acid [52]. Dodecanedioic acid, undecanedioic acid (ethyl acetate, methanol and water leaf extracts), and hexadecanedioic acid (ethyl acetate and methanol leaf extracts) were found in *A. leiocarpus* by HPLC-ESI-MS experiments [46].

5. Pharmacological activity

5.1. Antibacterial activity

There have been many scientific studies supporting the use of *A. leiocarpus* in African traditional medicines in treating various microbial infections including the eradication of oral pathogens, *Mycobacterium* and *Salmonella*. The methanol extract of the root – containing flavonoids and stilbenes such as **(22), (23), (24), (25)** and **(26)** – was found to show high potential for antibacterial activity against *Micrococcus luteus, Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus epidermidis* (MIC: 39.06 μg/mL) [43]. *Salih* et al. [41] investigated the antimycobacterial effects of *A. leiocarpus* used to treat tuberculosis in Sudan. Extracts from the plant's root showed activity against *Mycobacterium smegmatis* (MIC: 625–5000 μg/mL). Fractions with low MIC values were specifically found to have a high concentration of phenolic molecules which include **(2)**, acetylated ellagic acid derivative and dimethyl-ellagic acid xyloside. Extracts from leaves and stems showed activity against *P. aeruginosa* and *S. aureus* isolated from swabs collected from dental patients at General Hospital, Minna, Nigeria [56]. The food preservative and antibacterial effects of water and ethanol bark extracts were examined on isolated *E. coli*, *Salmonella* species, and *S. aureus*, and zones of inhibitions ranging from 13.5 ± 0.50 mm to 24.0 ± 2.00 mm were reported at 2000 μg/mL [57]. Ali et al. [58] demonstrated antimicrobial effects of the stem bark extracts against some of the seventeen microbes tested (zones of inhibition: 18–30 mm; MIC: 5–20 mg/mL; MBC: 10–40 mg/mL). A chromatographic isolate from the extract also had activity against the bacteria including methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *Enterococci* (VRE), *Candida albicans, C. krusei*, *C. tropicalis, Coryenbacterium ulcerans*, *E. coli*, *Klebsiella pneumonia, Proteus mirabilis*, *P. aeruginosa, Shigella dysenteriae*, and *Streptococcus faecalis*, *Salmonella typhi* (zones of inhibition: 23–34 mm; MIC: 12.5–25 μg/mL; MBC: 25–100 μg/mL). Methanol leaf extract used in Ghanian folk medicine showed concentration-dependent activity in wounded albino Wistar rats using excision wound model [59]. The methanol leaf extract had activity against *Citrobacter specie*, *E. coli*, *K. pneumonia,* and *S. aureus* using the agar well diffusion assay (zones of inhibition: 8.79 ± 0.2–10.9 ± 0.2 mm) [60]. Dayok et al. [61] screened the leaf extract against three bacterial strains (*P. aeruginosa, S. aureus, S. mutans*) which gave zones of inhibition of 10–23 mm. The methanol leaf extract was active against clinical isolates *K. pneumoniae*, *P. aeruginosa*, *P. vulgaris,* and *S. aureus* by disc diffusion method (18.27 ± 0.12 mm to 24.58 ± 0.13 mm) [62]. Elsiddig et al. [63] compared the antimicrobial effects of the leaf, root, and stem bark extracts against seven microorganisms: *A. niger*, *C. albicans, E. coli, K. aerogens, P. aeruginosa, S. typhi,* and *S. aureus*. The highest antibacterial as well as antifungal activities were found in the ethyl acetate leaf extract against *S. aureus* and *A. niger* (zones of inhibition, 27 mm, and 24 mm, respectively). The *in vitro* bacteriostatic effect of methanol-extracted leaf was reported on clinical strains of *E. coli, K. pneumoniae*, *P. aeruginosa,* and *S. aureus* (zones of inhibition: 8 ± 0.9–21 ± 0.5 mm [64]. The ethanolic root extract was tested against ten strains of *E. coli* isolated from blood culture, endocervical swab, ear swab and urine. The bacteria, through agar well diffusion method, showed susceptibility to the extract with varying zones of inhibition (17.90 ± 0.14 to 31.90 ± 0.14 mm) at different microbial inoculum loads (10^{-1} to 10^{-5} cfu/mL) [65]. Konaté et al. [66] studied the antimicrobial potential of acetone extract by agar diffusion and micro-well dilution assays against *B. cereus, E. coli, P. mirabilis, Salmonella typhimurium* and *S. aureus* (MIC: 390.63–1560 μg/mL). More recently, aqueous acetone extract of the stem bark that local people in Burkina Faso use to treat avian salmonellosis showed antibacterial activity against four *Salmonella* strains (MIC: 1.563–12.5 mg/mL) [67]. *A. leiocarpus* leaf used in the management of gastrointestinal diseases was extracted with dichloromethane, methanol, and water. These extracts were tested on nineteen strains of *Helicobacter pylori* by agar diffusion method. At 6 h of exposing the bacteria to the extracts at 0.32 mg/mL, the aqueous root and stem bark extracts produced a 100% kill. Susceptible strains had MIC and MBC values of 0.08–1.25 mg/mL and 0.16–2.5 mg/mL, respectively [68]. These extracts also demonstrated activity on five non-tuberculous *mycobacteria* strains (MIC: 0.3125–2.5 mg/mL; MBC: 1.25–10 mg/mL) [69]. Strains of *M. tuberculosis* and *M. bovis* were shown to be susceptible to crude methanolic extracts of root and bark by the broth microdilution method. Two silica gel and Sephadex chromatographed isolates from the active *n*-hexane fraction were found to exhibit significant antimycobacterial activity (MIC: 4.7 and 7.8 μg/mL) [70]. The crude methanol extracts of the stem bark exhibited broad growth inhibitory effects of clinical isolates of *B. subtilis, E. coli, Neisseria gonorrhoea, P. aeruginosa, S. typhi, S. aureus,* and *S. pyogenes* with MIC values of 0.3 to 0.4 mg/mL [71]. MIC values between 0.213 and 5.0 μg/mL were reported for the terpene-containing stem bark fractions when tested against strains of *E. coli and P. aeruginosa,* and *S. aureus* [72]. Antibacterial activity of extracts obtained from the plant's stem bark was evaluated against strains of respiratory tract infectious microorganisms including *E. coli, K. pneumoniae, K. oxytoca, K. ozaenae,* and *Pantoea agglomerans* by disc diffusion and Epsilometer test (*E*- test) assays. *E. coli, Klebsiella spp.*, and *P. agglomerans* were susceptible to aqueous and butanol extracts (zones of inhibition: 17–23 mm; MIC: 100 mg/mL; MBC: 200 mg/mL) [73].

Ouedraogo and Kiendrebeogo [74] studied the antiquorum sensing activity of the methanol stem bark extract used in Burkinabé traditional

medicine to treat infected burn wounds using the reporter strains *Chromobacterium violaceum* CV026, *P. aeruginosa* PAO1 and its derivatives. Through down-streaming the *rhlR* gene, the extract inactivated the quorum sensing mechanism of PAO1, and subsequently reduced pyocyanin production. Guineans use the extract of the stem bark in treating sexually transmitted infections. This extract showed activity against some bacterial strains (MIC: 125 μg/mL for *B. cereus*, *K. pneumoniae* and *S. aureus*) [75]. *A. leiocarpus* used in the traditional medicine of Mali for managing respiratory infections was investigated against clinical isolates of *Haemophilus influenzae, S. aureus, S. pneumoniae, S. pyogenes,* and *Moraxella catarrhalis* using disc-diffusion method. MIC was found between 7.8 μg/mL and 125 μg/mL [76]. Sore et al. [77] estimated MIC value of 0.86 mg/mL (by agar diffusion assay) for the leafy twigs extract of *A. leiocarpus* against the clinical isolate *of S. aureus. S. aureus.* Taiwo et al. [78] reported potent activity of the root extract (used as a chewing stick in Nigeria) against methicillin-resistant *S. aureus*, vancomycin-resistant *Enterococcus*, and multidrug-resistant *Burkholderia cepacia* and *P. aeruginosa.*

A similar study on ethanolic root (chewing stick in Benin Republic) gave MIC and MBC values between 0.195 and 12.500 mg/mL against *Enterococcus faecalis* ATCC 10240, *E. coli* ATCC 25922, *P. mirabilis* ATCC 24974, *P. aeruginosa* ATCC 27853, and *S. aureus* ATCC 29223 [79]. At 25 mg/mL, acetone stem extract inhibited the growths of the clinical isolates of *E. coli*, *Klebsiella* species, *Proteus* species, *P. aeruginosa,* and *S. aureus* using disc diffusion assay. Alpha-hemolytic *Streptococci* was observed to be resistant to the extract. Other bacteria showed diameters of zone of inhibition that ranged from 5 mm for *Klebsiella* species to 15 mm for *S. aureus* [80]. Soxhlet methanol extract of the leaf showed broad growth inhibition of *E. coli, P. aeruginosa,* and *S. aureus* using disc diffusion bioassay (MIC: 90 mg/mL) [81].

5.2. Anthelminthic activity

Ellagic acid **(7)** from *A. leiocarpus* was found to be active against the free-living nematode *C. elegans* and bovine filarial nematode *O. ochengi* (IC_{50}, 30–90 μM) [18]. The cattle nematode *O. ochengi* and free-living nematode *C. elegans* (Levamisole, ivermectin and albendazole-resistant mutant strains) were incubated with different concentrations of the ethanolic leaf extract and the effects on survival of the organisms were monitored after every 12 to 96 h. LC_{50} values of 0.06 mg/mL (*O. ochengi* microfilaria, adults), 0.09 mg/mL (*C. elegans* wild-type) after 24 h and 0.44 mg/mL after 48 h, and moderate potent activity in resistant strains (LC_{50} values, 0.27 mg/mL–1.5 mg/mL after 48 h) were observed [82]. Another study incubated worms with varied concentrations of DMSO-–ethanol-dissolved extract of the plant for 48 h and 72 h with LC_{50} (mg/mL) values of 0.62 and 0.38, respectively, against *C. elegans* [83]. Adama et al. [84] studied the anthelmintic effect of the leaf extract on the three life-cycle stages (eggs, first-stage larvae and adults) of *Haemonchus contortus* of sheep in Burkina Faso using egg hatch assay, embryonated egg assay and adult inhibition of motility assay. The effect was found to be concentration-dependent for both egg hatching (ED_{50}, (409.5 μg/mL) and first-stage larvae (ED_{50}, 362.3 μg/mL) but not for adult worms. Egg hatch inhibition assays and larval viability assays against *H. contortus* were conducted to determine the leaf extract (acetone) and fractions' ovicidal and larvicidal effects. The extract and fractions inhibited the eggs and killed the larvae in concentration-dependent way with LC_{50} ranged from 0.09318 to 0.3597 mg/mL for eggs and 0.1295 to 0.5085 mg/mL for adult worms [85]. Similarly, ethanol leaf extract collected in Northern Cameroon had dose-dependent anthelmintic potency on eggs and effective larvae of *H. contortus* [86]. The controlled and faecal egg count reduction tests were used to infect sheep with gastrointestinal nematodiasis. Infected sheep were ingested with aqueous extract of the leaf of *A. leiocarpus*. A dose-dependent decrease in faecal egg count was observed with the extract when compared to the untreated control. Results of the controlled test showed that sheep treated for three consecutive days with 400 mg/kg of the extract had fewer worms recovered from their gastrointestinal tracts than untreated sheep [87]. An 80 mg/kg of the ethanol leaf extract given orally reduced faecal egg numbers (81%) and adult worm-burdens (87%) against *Cooperia curticei* (100%), *H. contortus*, *Gaigeria pachyscelis* (90%), *Oesophagostomum columbianum* (95%), *Strongyloïdes papillosus* (100%), *Strongyloïdes papillosus* (100%), *Trichostrongylus axei* (67%), *Trichostrongylus colubriformis* (82%), and *Trichuris globulosa* (79%) in nematode-infected sheep [88]. The aqueous extract of the leaf, according to Agaie and Onyeyili in 2011, dose-dependently prevented eggs of the gastrointestinal strongyles of sheep from hatching [89]. The bark extract of the plant gave 60% deparasitization against adult *Nippostrongylus braziliensis* in rats at non-poisonous doses [20]. Aqueous and organic extracts from various parts of the plant showed evidence of anthelmintic activity against wild-type and the levamisole-resistant strain (LD_{50},18–24 mM) of *C. elegans* [90].

5.3. Antiprotozoal activity

There are a few review articles on *A. leiocarpus* as a potential therapeutic agent for protozoal diseases which covered important parasitic diseases such as onchocerciasis, leishmaniasis, lymphatic filariasis, schistosomiasis, and trypanosomiasis [4,91,92]. In an ethnobotanical survey by Zongo et al., farmers in Gaongho's pastoral area (Burkina Faso) identified diseases (accounting for 86.2% of which African Animal Trypanosomiasis accounted for 96.7%) as their primary constraint in ruminant rearing [23]. Testing *A. leiocarpus* for its potential molluscicidal activity did not show significant toxic effects on the egg masses or adult *Biomphalaria pfeifferi*, the host of *Schistosoma mansoni* in Nigeria [93]. Suppressive and repository tests were conducted *in vivo* to determine the antitrypanosomal property of the methanol bark extracts of *A. leiocarpus* and *K. senegalensis* using *Trypanosoma brucei brucei*-infected rats. The results showed that a threefold amount of *K. senegalensis* to *A. leiocarpus* proved more effective both as prophylactic and in maintaining the rats' PCV [94]. Germicidal and amoebicidal effects of the methanol and petroleum ether leaf extracts were investigated using *Entamoba histolytica* and *Giardia lamblia*. At 1000 ppm, the extracts exhibited activity ranging from 67.28% to 77.02% mortality for *G. lamblia* after 72 h, and 61.35% to 70.06% mortality for *E. histolytica* within 72 h [64]. Séverin et al. tested the aqueous leaf extract for its potential to prevent and cure coccidiosis by dividing 100 one-day-old Hubbard chicks into 4 groups after 7 days of acclimatization: Group A were control birds; group B was orally infected with 10.000 sporulated oocysts of *Eimeria tenella*; group C was infected and treated with 10 g/L of the extract; and group D was infected and treated with the positive reference 0.2 g/L of Vetacox S®. The study indicated that the extract appreciably lowered oocyst number and lesion score in the treated group compared to the untreated group [95]. Tauheed et al. investigated synergism in the antitrypanosomal potential of *A. leiocarpus* combined with *K. senegalensis* compared to a single drug treatment. Parasite-loaded blood containing 10^8 *T. congolense* cells and 50 μL of different concentrations of *A. leiocarpus* and *K. senegalensis* were incubated in a 96-well microtitre plate. Mice were inoculated with the incubated mixture after the parasites' complete immobility had been achieved. The parasitaemic rodents were treated with 500 mg/kg of single and combined extracts for 7 days. The combined group remarkably decreased the levels of parasitaemia and malondialdehyde, maintained higher PCV than the control group, and none of the mice developed parasitaemia within one month of observation [96].

5.4. Antifungal activity

Among five Togolese Combretaceae plants tested for antifungal activities, the hydroethanolic extract of *A. leiocarpus* leaf gave IC_{50} between 0.25 mg/mL and 4 mg/mL against a panel of yeast and filamentous fungi which include *A. fumigatus, Botrytis cinerea, C. albicans, C. krusei, C. parapsilosis, C. tropicalis, C. zeylanoides, Cladosporium cladosporioides, Cryptoccocus neoformans, Geotrichum candidum,*

Microsporum gypseum, M. nanum, Rhodotorula rubra, Trichophyton mentagrophytes, Trichoderma viride, and *Trichophyton rubrum* [97]. The leaf and bark materials extracted with water exhibited *in vitro* inhibitory effect against *A. nigeri* and *Fusarium oxysporium* isolated from vegetables [98]. Odumosu et al. conducted an antifungal study (using agar well diffusion assay) on the methanol stem extract against three *Candida* species resulting in MIC values that ranged from 3.125 mg/mL to 100 mg/mL [99]. In Sudan, El Egami et al. [100] used agar diffusion assay to investigate the antifungal effect of *A. schimperi* along with other Sudanese plants against *C. albicans*, and *Saccharomyces cerevisiae.* The methanol extract of the stem bark produced an MIC value of 0.18 μg/mL against *S. cerevisiae* [100]. The fungicidal activity of the aqueous leaf extract on *Curvularia sp.* obtained from *Jatropha curcas* L. showed the extract to have a concentration-dependent inhibitory effect on mycelial growth [101]. Using the radial growth technique, the extracts (aqueous, chloroform, ethanolic, ethyl acetate and methanol) from *A. leiocarpus* root showed significant antifungal effects on *A. fumigatus, A. niger, M. audouinii, Penicillium* species and *T. rubrum.* MIC values of the extracts were found to range from 0.03 μg/mL to 0.06 μg/mL and MFC ranged from 0.04 μg/mL to 0.08 μg/mL [149].

5.5. Antimalarial activity

Ohashi et al. [102] screened 112 extracts of medicinal plants in Ghana for antiplasmodial activities, and the leaf extract (50% ethanol) of *A. leiocarpus* had IC_{50} of 18.32 μg/mL against *P. falciparum* using the fluorescence-activated cell sorting (FACS) method [102]. The methanol extract of the stem was studied *in vivo* for antiplasmodial activity, oxidative stress, and lipid profile against *P. berghei berghei*-infected mice. Mice were divided into five groups, four of which were infected with the parasite. The treated group with 100 and 200 mg/kg body weight of the extract had high parasite clearance in their blood [103].

In addition to single testing of *A. leiocarpus* extracts against malaria-causing parasites, some studies attempted to combine *A. leiocarpus* with other plant extracts with ethnopharmacological relevance in malaria treatment. In an antiplasmodial study by Ndjonka et al., the single extract of *A. leiocarpus* bark produced an IC_{50} value of 18.8 ± 2.8 μg/mL against *P. falciparum* 3D7 in 96-well microtiter. However, synergistic effects were observed when combined with *Phyllanthus muellerianus* (Kuntze) Excell (leaf), *K. senegalensis* (bark), *Euphorbia hirta* L. (leaf) and *Steganotaenia araliacea* Hochst. (leaf) (1:1) with lower IC_{50} values of 10.8 ± 1.0, 12.5 ± 2.7, 16.5 ± 2.2, and 18.6 ± 2.8 μg/mL, respectively [55]. Akanbi [104] combined methanol bark extracts of *A. leiocarpus* and *Terminalia avicennioides* Guill. & Perr. and investigated the parasite clearance effect (at doses of 100, 200 and 400 mg/kg body weight) on the blood of *P. berghei*-infected mice. After four days of treatment, it was observed that parasite clearance was greatest in the group that received 400 mg/kg and lowest in the one that 100 mg/kg. *A. leiocarpus* stem bark was also combined with the stem bark extract of *Prosopis africana* (Guill., Perrott, & Rich.) (Taub.) to evaluate their antiplasmodial effect in infected rodents. Swiss albino mice were infected with chloroquine-sensitive *P. berghei* (NK 65). The treated groups were given extract at the doses of 200 and 400 mg/kg body weight at the early stage of infection while 100 and 400 mg/kg body weight of the extract were given to mice in the established stage of plasmodial infection. The combined aqueous extract of the two plants reduced parasitaemia in early infection by 50% at 200 mg/kg and 69% at 400 mg/kg body weight while the extract suppressed parasitaemia by 55% to 78% at 100 to 400 mg/kg body weight in established infection [105].

The ethyl acetate extract of the leaf had a significant antiplasmodial effect (IC_{50}, 10 μg/mL) using the *in vitro* microculture radioisotope technique. The isolated flavonoids from the active extract were evaluated against the multidrug pyrimethamine/chloroquine-resistant strain *P. falciparum* k1 (Table 3) [47]. The methanol leaf extract gave IC_{50} of 4.9 μg/mL in an *in vitro* investigation against the multi-resistant strain (W2) of *P. falciparum* [106]. Shuaibu et al. evaluated the *in vitro*

Table 3
Biological activities of some compounds from *A. leiocarpus.*

Compounds	Activities	*In vitro/in vivo* models	References
Castalagin **(5)**	Antiprotozoal activity	*Leishmania aethiopica* (IC_{50}, 55 μg/mL), *L. amazonensis* (IC_{50}, 65 μg/mL)	[44]
	Antiplasmodial activity	*Plasmodium falciparum* 3D7 (IC_{50}, 11.3 μM) and *P. falciparum* K1 (IC_{50}, 10.3 μM)	[53]
Ellagic acid **(7)**	Anthelmintic activity	*Caenorhabditis elegans* and *Onchocerca ochengi* (IC_{50} = 30–90 μM)	[18]
	Anthelmintic activity	*O. ochengi* (microfilariae), *O. ochengi* (adults), *C. elegans* (wild-type), and anthelmintic-resistant strains of *C. elegans* (albendazole-resistant strain, CB3474; levamisole-resistant strain, CB211 and ZZ16; and ivermectin-resistant strains, VC722 and DA1316. LC_{50} values ranged from 0.03 mM to 0.96 mM.	[54]
	Antiplasmodial activity	*P. falciparum* 3D7 IC_{50} 2.88 μM	[55]
	Antiplasmodial activity	*P. falciparum* 3D7 (IC_{50}, 40.2 μM) and *P. falciparum* K1 (IC_{50}, 37.1 μM)	[44]
Flavogallonic acid **(13)**	Antiplasmodial activity	*P. falciparum* 3D7 (IC_{50}, 18.9 μM) and *P. falciparum* k1 (IC_{50}, 8.35 μM)	[53]
Gallic acid **(10)**	Anthelmintic activity	*C. elegans* levamisole-resistant strain (ZZ16, LC_{50}, 9.98 mM)	[54]
	Antiplasmodial activity	*P. falciparum* 3D7, LC_{50}, 71.53 ± 8.96 μM	[55]
Gentisic acid **(11)**	Anthelmintic activity	*C. elegans* ivermectin-resistant strain (DA1316, LC_{50}, 10.62 mM), and albendazole-resistant strain (CB3474, LC_{50}, 7.81 mM)	[54]
	Antiplasmodial activity	*P. falciparum* 3D7, LC_{50}, 49.76 ± 0.32 μM	[55]
Procyanidin B2 **(21)**	Antiplasmodial activity	Microculture radioisotope technique using *P. falciparum* k1 IC_{50}, 5.3 μM	[47]
Punicalagin **(9)**	Anthelmintic Activity	*C. elegans* LD_{50} of 1.69 mM (24 h) and LD_{50} of 0.98 mM (48 h)	[45]
Quercetin **(15)**	Antiplasmodial activity	Microculture radioisotope technique using *P. falciparum* k1 IC_{50}, 6.6 μM	[47]
Rutin **(16)**	Antileishmanial activity	*L. donovani* IC_{50} = 1.6 μM	[47]
3,4,3′-Tri-*O*-methylflavellagic acid 4'-*O*-glucoside **(4)**	Antibacterial activity	*In vitro* agar dilution method at a concentration of 8.3 x $l0^{-3}$ μg/mL inhibited the growth of *Escherichia coli*	[39]

antiplasmodial potential of methanol extracts of sixteen plants including *A. leiocarpus* by a fluorometric assay using PicoGreen. *A. leiocarpus* extract gave an IC_{50} value of 10.94 μg/mL against chloroquine-sensitive 3D7 and 13.77 μg/mL against chloroquine-resistant K1 strains of *P. falciparum* [53]. The methylene chloride extract of the leaf also displayed antiplasmodial properties (IC_{50}, 3.8 μg/mL) *in vitro* using the microculture radioisotope technique which is based on the uptake of [3H]hypoxanthine by K1-resistant strain of *P. falciparum* [107].

5.6. Antitumour activity

The methanol root extract of *A. leiocarpus* was subjected to the MTT assay against breast cancer (MCF-7) and rhabdomyosarcoma (RD) cell lines. Significant activity was observed (RD: 13.82 ± 2.05; MCF-7: 25.64 ± 7.58 μg/mL) [108]. The antiproliferative activity of *A. leiocarpus* used as an antidiabetic in Nigeria was studied on liver (HepG2), colon (Caco2), and skin (B16-F10) cancer cell lines with the use of Sulforhodamine B (SRB) staining assay. The extract significantly inhibited B16-F10 (GI_{50} = 50 μg/mL) [109]. The cytotoxicity of six extracts from the leaf and stem bark was studied using an MTT assay against colon (HCT-116) and MCF-7 cell lines. The *n*-hexane and ethanol extracts of the plant's bark were moderately cytotoxic against HCT-116 (% cell inhibition, 61.24% and 58.25%, respectively). The antiproliferative activity of the ethanolic leaf extract was investigated by the *in vivo* human tumour xenograft model against HCT-116. NCR NuNu nude mice bearing tumours were given ethanolic extracts of leaves orally for 35 days. A dose-dependent decrease in tumour size was observed in the treated animals with tumour growth inhibition ($\Delta T/\Delta C$) of 7.54% at 200 mg/kg and 2.97% at 400 mg/kg. Using Rat Aorta Ring Assays (RARAs), *n*-hexane extract of the bark exerted the strongest anti-angiogenic activity (89.56%), followed by ethanol extract of the leaves (87.12%) [110].

Olugbami et al. reported laboratory-based results of the antitumour activity of ethanol leaf extract in comparison with resveratrol. Cytotoxicity was estimated using the fluorometric propidium iodide (PI) staining assay while the antioxidant status, caspase activities, adenosine triphosphate (ATP) levels, and mitochondrial integrity of HepG2 cell were determined using fluorometry/luminometry. The extract was found to modulate HepG2 liver carcinoma proliferation in a concentration- and time-dependent manner after 72 h of treatment, causing cell death and necrosis at lower and higher concentrations respectively; and somewhat mitotoxic at the highest concentration tested [111]. Various concentrations of the aqueous root extract of *A. leiocarpus*, *T. avicennioides* and 1:1 mixture of both were incubated with Ehrlich ascites carcinoma cell lines for 3 and 24 h. It was then shown that the extracts strongly decreased the percentage viability of the cells in a dose- as well as a time-dependent way [112].

5.7. Antidiabetic activity

A. leiocarpus extracts have demonstrated antidiabetic effect in different diabetic models. *In vivo*, Esievo et al. [113] investigated antidiabetic activity of the ethanolic stem bark extract in four groups of three dogs. Group 1: control, non-diabetic dogs orally fed with normal saline at 2 mL/kg body weight; Group 2: negative control, diabetes-induced but left untreated dogs; Group 3: positive control, diabetes-induced and treated with insulin at a dose of 0.5 IU/kg body weight; Group 4: diabetes-induced and treated with extract at 1000 mg/kg body weight. All groups were assessed for free serum sialic acids (FSSA) and erythrocyte surface sialic acids (ESSA) before and after hyperglycaemia induction. FSSA was observed to increase in the untreated group to and plateau in the third week at 61.8 ± 0.41 μg/mL. The extract effectively attenuated the level of FSSA as the value decreased to 21.4 ± 0.78 μg/mL in an extract-treated group compared to the insulin-treated group which decreased to 22.3 ± 1.55 μg/mL [113]. A similar *in vivo* study investigated the antidiabetic effects of ethanolic stem bark extract in alloxan-induced acute type 1 diabetes mellitus extending into chronicity using twelve adult Nigerian indigenous dogs divided into 4 groups. Hyperglycaemia was ensured in the diabetic dogs and the groups treated with the extract significantly reduced blood glucose in a manner comparable with the positive reference insulin ($P < 0.002$) [114].

Another *in vivo* study employed an oral glucose tolerance test (OGTT) to evaluate the antihyperglycemic activity of the hydroalcoholic extract and fractions of *A. leiocarpus* root in mice. The crude extract and all fractions were found to significantly ($p < 0.0001$) decrease hyperglycaemia in treated mice compared to the control group after 30 min of glucose overload. In addition, *A. leiocarpus* extracts and fractions adsorbed glucose *in vitro* and inhibited intestinal glucose absorption *ex vivo* [115]. This extract and fractions were also examined for their effects on triglyceride synthesis using the *in vivo* fructose overload test in mice. The serums of the extract- and fraction-treated mice were analysed for triglycerides, total cholesterol high-density, low-density, and very-low-density lipoproteins. Triglyceride was also extracted from their liver. The extract and fraction (supernatant) (100 mg/kg) decreased triglycerides, VLDL and, cholesterol in the serum but more remarkably in the liver compared to the positive control [115]. Recently, an intraperitoneally administered streptozocin-induced diabetes mellitus model in Sprague Dawley rats under a fructose-enriched fat diet was used to demonstrate the antihyperglycemic potential of the hydroalcoholic extract and fractions of *A. leiocarpus* root. After 7 days of treatment, the blood glucose levels in the treated group were found to reduce significantly compared to the control groups. In addition, a decrease in the serum levels of cholesterol and triglycerides was observed in the treated group [116]. Omeje et al. used the alloxan-induced diabetic model in rats at different oral doses (100–500 mg/kg/day) to study the antidiabetic potential of the leaf and root extracts. The extracts displayed dose-dependent antidiabetic activity up to a dose of 200 mg/kg with reported glucose lowering values of 52.69 ± 5.99% at 12 h and 66.61 ± 5.79% at 24 h compared to 24.39 ± 1.54% at 12 h and 38.79 ± 4.06% at 24 h for the positive control [117]. The ethanolic leaf extract was also examined for its blood glucose-reducing ability and effects on other biochemical parameters in alloxan-induced diabetic adult male Wistar albino rats. Diabetes induction was done by intraperitoneally injecting rats with alloxan monohydrate at 150 mg/kg body weight single dose, and extracts were administered for 14 days. The results showed that the fasting blood glucose levels were decreased in extract-treated groups (62.2 ± 18.4 mg/dL) compared to the control diabetic group (73.8 ± 8.2 mg/dL). Total cholesterol, triglycerides, and high-density and low-density lipoproteins were also found to reduce in treated rats compared to the control group [118]. Oboh et al. examined the inhibitory potential of the aqueous stem bark extract on some enzymes including α-amylase and α-glucosidase. The extract demonstrated good activity producing an IC_{50} value of 223.41 μg/mL against α-amylase [119].

5.8. Antioxidative activity

DPPH free radical scavenging and ferric reducing activity of the methanol leaf extract of *A. leiocarpus* showed that it had a high scavenging ability (% DPPH inhibition, 95.86 ± 0.1%; ascorbic acid, 96.78 ± 1.9%) [60]. Konaté et al. reported an IC_{50} of 1.07 ± 0.06 μg/mL for the DPPH free radical scavenging activity of the aqueous acetone extracts and 21.87 ± 0.07 mmoL AAE/g extract in the ferric reducing ability of plasma (FRAP) experiment [66]. The methanol stems bark extract was shown to exhibit significant DPPH free radical scavenging activity with the IC_{50} value of 1.82 ± 0.07 μg/mL as compared to the reference antioxidant agent quercetin (IC_{50}, 1.40 ± 0.15 μg/mL); and the ferric reducing power as 4.29 ± 0.19 μM AAE/g while that of antioxidant reference was 7.66 ± 0.39 μM AAE/g [74]. The cytotoxic ethanol leaf extract also showed a significant DPPH free radical scavenging effect with IC_{50} value of 29.87 μg/mL. The total phenols content, expressed as gallic acid equivalent in mg/mL of extracts, was in the range of 14.85 ± 0.02 and 497.74 ± 0.01 GAE for six extracts from the

leaf and stem bark of the plant, while the highest amount of flavonoids, expressed as quercetin equivalents in 6 mg/mL of extracts, was found in the aqueous (110.350 ± 0.0 mg/g) and ethanol (78.642 ± 0.01 mg/g) extracts of the leaf [110]. The DPPH scavenging assay of the hydro-alcoholic extract and fractions of the root resulted in IC_{50} values ranging from 23.3 ± 0.35 μg/mL to 72.7 ± 0.70 μg/mL; a ferric reducing power that was concentration-dependent was also observed for the extract and fractions [120].

DPPH free radicals were used as a substrate to determine *A. leiocarpus* antioxidant activities, as well as the FRAP assay to determine its reducing ability. The *in vitro* DPPH free radical scavenging activity of the methanol root extract, though in a dose-dependent way, was comparable to that of positive reference (ascorbic acid) [121]. Olugbami et al. [122] used various assay methods to investigate the antioxidant effect of the ethanolic stem bark extract. The methods include DPPH free radical scavenging (2,2-diphenyl-1-picrylhydrazyl), phosphomolybdate, β-carotene bleaching, ferric reducing, and hydroxyl radical scavenging assays. The extract showed high antioxidant activities when compared with the controls.

5.9. Improving erectile dysfunction

Phosphodiesterase 5 enzyme (PDE5) plays an important role in erectile dysfunction pathophysiology, and its activity increases which leads to reduced 3–5-cyclic guanosine monophosphate (cGMP) levels [123]. Therefore, most studies focus on the inhibitory potential of medicinal plants on PDE5. The stem bark extract of *A. leiocarpus* was evaluated for its aphrodisiac activity using paroxetine-induced sexual dysfunction in forty-two male Wistar rats divided into seven groups. The treated group was given 50 and 100 mg/kg of the extract. All the animals were subjected to sexual behaviour tests after 21 days. Biochemical assays such as arginase, acetylcholinesterase, PDE5, malondialdehyde, lipid peroxidation and nitric oxide were conducted on the penile tissue homogenate. It was observed that the treatment with *A. leiocarpus* extract reverted the altered sexual behaviour in male rats and boosted antioxidant status by decreasing phosphodiesterase-5, arginase, acetylcholinesterase activities, and malondialdehyde levels [124]. *In vitro* evaluation of the activity of purified vascular PDE isoenzymes (PDE1-PDE5) of the aqueous extract of *A. leiocarpus* stem bark was conducted with penile tissue homogenate, and it gave an IC_{50} value of 174.19 μg/mL. The IC_{50} of dichloromethane fraction on isolated PDE5 was found to be 7.6 ± 3.5 μg/mL [125]. The effects of the extract of *A. leiocarpus* were also studied on PDE-5 and arginase enzymes [126]. The extract inhibited enzymes' activities in a dose-dependent way with an IC_{50} value of 174.19 μg/mL in PDE-5 assay and 38.01 ± 0.47 μg/mL in arginase-assay. *In vivo,* the aqueous extract of the plant's stem bark was examined for its inhibitory potential on phosphodiesterase-5 and arginase enzymes using male Wistar albino rats. The extract was found to show strong inhibition of the enzymes with IC_{50} values of 174.19 μg/mL and 38.01 μg/mL, respectively [119].

5.10. Antihypertensive activity

A four-week oral dosing of aqueous stem bark extract of *A. leiocarpus* (50 mg/kg) to L-NAME-induced hypertensive Wistar rats was conducted to investigate its effects on blood pressure. High blood pressure was produced in the rats by daily oral administration of L-NAME (40 mg/kg) for two weeks, this led to increased systolic blood pressure from 115.8 ± 7.9 mmHg to 153.5 ± 4.6 mmHg. Lower systolic blood pressure (108.8 ± 2.7 mmHg) after four days of treatment was noted in the treated group compared with normotensive rats. This suggested the antihypertensive effect of the extract [127].

5.11. Anti-ulcer activity

In vivo, ulcerative colitis was induced in rats by intrarectally administration of 1 mL of 4% acetic acid. The rats were divided into distilled water group (negative control), dexamethasone group (positive control), 100 mg/kg body weight extract and 200 mg/kg body extract groups. All test substances were administered for 7 days. The blood and colon of the rats were collected for oxidative stress, haematological and histological examinations after the treatment period. It was observed that the treated groups had reduced diarrheal stools and body temperature compared to the untreated control group. Also, a significant decrease in the number of gross colon lesions, nitric oxide, malondialdehyde levels in the colon and blood was observed. This study provided support for the local use of the plant to treat ulcer-related symptoms [128]. The aqueous extract of the stem bark was also shown to possess a gastroprotective effect against ethanol-induced gastric ulcers in rats. Oral administration of the extract at doses of 100, 200 and 400 mg/kg body weight for 14 days reduced the mean ulcer score, ulcer index, percentage ulceration and preventive index induced by 70% ethanol in a dose-dependent way [129].

5.12. Anti-sickling activity

Egunyomi et al. reported that *A. leiocarpus* is a component of an antisickling recipe used by the Ibadan people of southwestern Nigeria to treat sickle cell anaemia (SCA). The anti-sickling activity of this recipe (containing 28 plants) was determined using a method which involves the inhibition of sodium metabisulphite-induced sickling of HbSS red blood cells that was collected from confirmed non-crises sickle cell patients. *p*-Hydroxybenzoic acid and normal saline were used as controls. Percentage inhibition of 63.4% was noted after 3 h of incubation [130].

5.13. Hepatoprotective and nephroprotective activity

In a study aimed at evaluating the hepatoprotective and nephroprotective potential of *A. leiocarpus* ethanol bark extract in CCl_4-injected rats, biochemical and histopathological evidence was found to support the use of the plant in Sudan to treat liver diseases. Liver sections of rats injected with CCl_4 showed the lay centrilobular vacuolations and necrotic hepatocytes while the extract-treated group showed less vacuolated hepatocytes and cellular regeneration. The tubular dilation with degenerative changes in tubular epithelium seen in the kidney photomicrographs of the control rats (CCl_4 treated group) was less pronounced in rats fed with *A. leiocarpus* extract. The activities of liver enzymes (AST, ALT, ALP) and kidney biomarkers levels (urea, creatinine) were also observed to be lower compared to the control group [131]. Altered levels of renal function biomarkers in potassium dichromate-induced nephrotoxicity in rats were restored by hydro-alcoholic extract and a fraction of *A. leiocarpus* root possibly *via* its antioxidant and anti-inflammatory activities [151].

5.14. Improving fertility

A dose-dependent significant ($P < 0.05$) increase in epididymal weight (about 0.3 g), mean sperm count (about 49.5%) and mean fast sperm motility with a corresponding significant reduction in slow motile sperm cells compared to the control groups were observed in *A. leiocarpus* extract-treated rats in a study investigating the pro-fertility potential of the aqueous leaf extract of the plant [132]. In support of the potential use of *A. leiocarpus* in fertility-related issues, Jibril et al. [133] found an appreciable increase in oestradiol and progesterone levels in the serum (19% higher than control) in animals treated with the aqueous stem extract. The extract also prolonged the di-oestrus and oestrus phases of rats' oestrous cycles in a dose-dependent manner when treated at doses of 200 mg/kg and 400 mg/kg.

5.15. Enzyme inhibitory activity

Orlando et al. [46] reported the enzyme inhibitory effects of various

aqueous and organic extracts from the leaf and stem bark of *A. leiocarpus* with acetylcholinesterase inhibitory activity ranging from 3.51 to 4.68 mg GALAE/g and butyrylcholinesterase inhibitory activities (0.45–4.0 mg GALAE/g). Aside from the Alzheimer's disease-related enzymes, the extracts also showed activity against enzymes related to skin hyperpigmentation such as tyrosinase (values ranging from 113.0 to 155.26 mg KAE/g) which is a copper-containing enzyme that catalyses the biosynthesis of skin pigments like melanin.

5.16. Antinociceptive and antipyretic activity

Acetic acid-induced writhing and tail immersion models were utilised to evaluate the anti-nociceptive activities of *A. leiocarpus* aqueous extract while Dinitrophenol and Brewer's yeast-induced pyrexia were used to evaluate the antipyretic activities in Wistar rats. The extract significantly ($p < 0.05$) decreased the induced pain and pyrexia in rats at doses of 200 and 400 mg/kg, in a manner comparable to aspirin control. The 400 mg/kg dose produced a reduction of abdominal constrictions in mice (84.5% inhibition) compared to aspirin (85.9%). In the tail immersion experiment, the extract at both doses also shielded the animals from the heat stimuli of the hot bath. The extract also suppressed the temperature induced by brewer's yeast which was sustained for up to 6 h in the animals [134].

5.17. Others

Laboratory experiments have also demonstrated other biological activities of extracts from *A. leiocarpus* which include antispasmodic, and geno-protective effects. Timothy et al. showed that extracts from *A. leiocarpus* have antispasmodic effects on isolated rabbit ileum. Effects of different concentrations of aqueous and ethanol extracts from the leaf and stem bark of the plant and acetylcholine were studied using an organ bath containing the ileum of a healthy rabbit. The effective dose that gave 50% biological response was extrapolated from the dose-response plot to be 1.58 mg/mL [135]. The micronucleus test was used to assess whether the hydroalcoholic root extract of *A. leiocarpus* had genotoxic and protective effects *in vivo* on mouse bone marrow cells. The extract was administered to mice (genotoxicity was induced by intraperitoneal cyclophosphamide administration) at concentrations of 250, 500 and 1000 mg/kg body weight daily for 7 days. Compared to the vehicle control group, the ratio of polychromatic erythrocytes (PCE) and frequency of micronucleated PCE (MNPCE) in the bone marrow cells of the mice did not significantly increase. There was, however, a significant rise in the incidence of MNPCE in the bone marrow cells of mice treated with cyclophosphamide. This study concluded that *A. leiocarpus* extract had protective effects against cyclophosphamide-induced DNA damage *in vivo* [136]. A recent study has shown that the oleanane-type triterpene and ellagitannin extracts of *A. leiocarpus* reduced pains and improved motor skills in sodium monoiodoacetate-induced osteoarthritic rats [154]. The *in vivo* investigation of the effects of the methanol stem bark extracts of *A. leiocarpus* against pentylenetetrazole-induced seizures/cognitive impairment in rats had been reported. Brain histology and oxidative stress biomarkers examinations revealed that the extract reduced seizure activity, retarded histological alterations, and ameliorated induced-oxidative stress [155].

6. Toxicity

Acute (Table 4) and sub-acute toxicity studies have been conducted on extracts of *A. leiocarpus* in laboratory animals using different routes of administration. Biochemical parameters such as alanine aminotransferase, aspartate aminotransferase, and bilirubin levels were examined in the liver and serum of *P. berghei*-infected mice. The levels of the enzymes were higher in a group treated with 200 mg/kg than those treated with 100 mg/kg. Administering doses higher than 200 mg/kg body weight of the extract in malarial treatment should be carefully monitored to prevent hepatotoxicity [137]. Similarly, Cyril-Olutayo et al. showed that the methanol bark extract of *A. leiocarpus* altered haematological indices (haemoglobin, red blood cells, packed cell volume, lymphocytes, and neutrophils) in *P. berghei*-infected mice [138]. Ahmad and Wudil [139] reported that the activities of alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase and bilirubin levels did not increase significantly in animal groups administered with up to 200 mg/kg body weight of aqueous stem bark extract of *A. leiocarpus* after 4 weeks of treatment [139]. A study by Bello et al. however, revealed that animals treated for six weeks with aqueous stem bark extracts were significantly elevated in the levels of alanine aminotransferase, aspartate aminotransferase, acid phosphatase, and lactate dehydrogenase, suggesting that animals ingested with 500 mg/kg body weight had some degree of liver injury [140].

Table 4
Toxicological studies: LD_{50} values (mg/kg body weight).

Extracts	Route of Administration	LD_{50} (mg/kg)	References
Aqueous and methanol stem bark	Oral	>5000	[143]
Aqueous bark and ethanol leaf extracts	Intraperitoneal	>1000	[135]
Aqueous leaf and ethanol bark extracts		283	
Aqueous stem bark	Oral	>5000	[129]
Aqueous leaf	Oral	>5000	[134]
Aqueous leaf	Oral	>5000	[132]
Aqueous leaf	Oral	2403.6	[144]
Aqueous leaf	Intraperitoneal	1400	[145]
Aqueous leaf	Oral	>5000	[146]
Acetone leaf	Oral	774.60	[147]
Aqueous stem	Oral	3807	[152]
	Intraperitoneal	126	

A mixture of *A. leiocarpus* and *T. avicennioides* (1:1 *w*/w) aqueous root extract reversed diethylnitrosamine-induced reductions in the levels of liver superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, glucose 6-phosphate dehydrogenase, glutathione in Wistar rats. Diethylnitrosamine also elevated the liver malondialdehyde level which the extract lowered to a level comparable to the animals fed with distilled water. The extract was, therefore, found to possess antioxidant, hepatoprotective and haemoprotective activities which compared favourably with the curcumin-treated rats [141]. However, another study reported a significant decrease in the activities of serum alkaline phosphatase, liver and serum aspartate aminotransferase, alanine aminotransferase and gamma-glutamyl transferase activities and chloride ions and an increase in liver and kidney alkaline phosphatase by the mixture of the extract (1:1) at doses of 250, 500 and 1000 mg/kg body weight of the extract [148]. Administration of the aqueous root extract of *A. leiocarpus* alone at 250, 500 and 1000 mg/kg body weight was also found to significantly ($p < 0.05$) decrease liver and kidney malondialdehyde, increase serum total protein, and serum bilirubin. Serum urea, sodium, potassium, chloride, and bicarbonate ions were also found to increase. However, the extract did not significantly change haematological parameters [142].

7. Future works and conclusion

Anogeissus leiocarpus (DC.) Guill. & Perr. is an important plant, which has been used traditionally to treat various ailments in Africa, and for other purposes such as construction and as a source of dyes for tinctorial practices. Studies which employ *in vitro* and *in vivo* models have substantially confirmed its traditional uses and reported biological activities include antibacterial, antidiabetic, antifungal, anthelmintic, antimalarial, antiprotozoal, antitumour and antiulcer activities. Bioactive compounds from *A. leiocarpus*, principally ellagitannins and other ellagic acid derivatives, flavonoids, and oleanane-type pentacyclic

triterpenes–and their biological actions have also been investigated.

Although various extracts from *A. leiocarpus* were active on both resistant and susceptible strains of bacteria, the bioactive components causing microbial growth inhibition were not reported. Future work should also establish the effectiveness of *A. leiocarpus* in attacking viral cells. There are needs also to establish its anti-asthmatic and antivenom potential as claimed by cattle rearers. Furthermore, the stem bark was the most investigated morphological part of *A. leiocarpus*. No study was found on the phytochemical and pharmacological profile of the seeds or the aerial part, for instance. Although traditional users of the plant mentioned the stem bark more frequently than the leaf, root and seeds in the various ethnobotanical surveys, other parts of the plant should also be extensively studied in the quest for novel compounds and/or novel biological activities.

In addition, of the over 100 (including fatty acids) compounds identified from *A. leiocarpus*, only a few have been tested for biological activity. Some ellagitannins, flavonoids, and triterpene saponins demonstrated anti-protozoal and antiplasmodial activities. However, most of the compounds are yet to be tested for biological activity. Further studies need to be carried out on some of these compounds which have not been linked to any biological activities or ethnopharmacological properties. Perhaps, the primary reason why most of the compounds have not been linked to biological activity is because they were tentatively identified by HPLC-DAD-MS analysis. Not isolating compounds by chromatographic techniques and elucidating their structures by spectroscopic techniques has the disadvantage of not making compound samples available for biological testing. To address this concern, enough quantity of compounds should be isolated from the plant to afford testing for biological activity *in vitro* or *in vivo*. In addition, the mechanisms of action of the isolated compounds should be studied.

Lastly, one of the main components of *A. leiocarpus* are tannins. Tannins are known to exhibit unfavourable pharmacokinetic profiles due to their hydrolytic susceptibility and their complex structures which make gastric absorption difficult. Ellagitannins slowly hydrolyse in the digestive tract to free ellagic acid, which is further metabolized by gut microbiota to urolithins. Urolithins are the primary bioavailable metabolites of dietary ellagitannin consumption. These small molecules have been shown to bind oestrogenic receptors, thereby exhibiting anti-breast cancer activity. Urolithins also possess antioxidant, anti-inflammatory, and antimalarial activity. Hence, rational design and synthesis of urolithin derivatives should be conducted in future studies as a way of avoiding endangering plant species and ensuring their conservation.

CRediT authorship contribution statement

Yemi A. Adekunle: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Babatunde B. Samuel:** Writing – review & editing, Supervision, Software, Methodology, Formal analysis, Conceptualization. **Lutfun Nahar:** Writing – review & editing, Supervision, Software, Methodology, Formal analysis, Conceptualization. **Amos A. Fatokun:** Writing – review & editing, Supervision, Software, Methodology, Formal analysis, Conceptualization. **Satyajit D. Sarker:** Writing – review & editing, Supervision, Software, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare no competing interest exists in the writing and submission of this manuscript.

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