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A review on ethnobotany, phytochemistry, and pharmacology of *Microdesmis keayana* and *Microdesmis puberula* (Pandaceae)

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ABSTRACT

Microdesmis keayana and *Microdesmis puberula* (Pandaceae) are two major plant species in the genus *Microdesmis*. They are dioecious shrubs, very similar in their morphology, botanical distribution, and medicinal uses, and native to most tropical and subtropical African regions. Traditionally, they are commonly used to treat erectile dysfunction, general body pain, snake bites, skin and intestinal infections, tumors, diarrhea, diabetes, obesity, headache, and migraine. This review is aimed to provide a compendium of ethnopharmacological and phytochemical information on the *Microdesmis* plants for future research and drug development initiatives. Relevant books and electronic databases were sourced during the literature review. Several phytochemical investigations resulted in the isolation and identification of about eight compounds from *M. keayana* and *M. puberula*, including four spermines and five spermidine alkaloids, and a quinoline, which were all isolated from the methanol and hydromethanolic root extracts of the two plants. *In vivo* and *in vitro* pharmacological studies of the plants showed aphrodisiac, antimalarial, antimicrobial, antioxidant, analgesic, antistress, and antisickling activities, which gave credence to their use in ethnomedicine. The plants can potentially be used for several disease conditions, including erectile dysfunction, malaria, infections, and pains, with a view to isolating bioactive lead compounds for drug development.

INTRODUCTION

Microdesmis keayana J.Leonard and *Microdesmis puberula* Hook.f. ex Planch. are two major species out of about 11 species found in the genus *Microdesmis*, Pandaceae (van Welzen, 2011). The plants are well spread in the tropical and subtropical African regions, including Ghana, Congo Republic, Ivory Coast, Nigeria, Sierra Leone (Royal Botanical Garden Kew, 2022), Burundi, Gabon, and Rwanda (Dounias, 2008). Both species are comparable in their morphology and medicinal uses, and in some regions, are confused as similar species (Alvarez Crus, 2008; Dounias, 2008). Besides their medicinal uses, the plants are important leafy vegetables with essential nutritional content eaten by some tribes as chew sticks by locals (Dounias, 2008) and browse plants for animals (Esonu *et al*., 2004; Okon *et al*., 2018; Umoh *et al*., 2004).

Local names of *M. keayana and M. puberula* vary throughout Africa due to ethnocultural diversity in the continent. Some *M. keayana* local African names include Sonoufoko (West Africa), Idi-apata, Aringo, Igi-ope (Yoruba), Mkpiri, Kpirimbo (Igbo), Amama, Erankpata (Esan), Ntanebit (Efik), Akpalata, Ingolongolo (Bayelsa), kawa (Boki), Babében evela (Diola), Gbihi, Kondgu (Kono), Kpendeile (Kissi), Bulon (Sherbro), and Efima (Anyi-Ndenye). *Microdesmis puberula* local African names include Sonoufoko (West Africa), Esunsun, Idi-apata, Aringo, Igi-ope, Igi ori apata (Yoruba), Mkpiri, Mbugbo, Kpirimbo (Igbo), amama, erankpata (Esan), Ntanebit (Efik), Akpalata, Ingolongolo (Bayelsa), Ofema (Ashanti), Nikee (Wonegizi), Dikota (Congo), and Mokula (Mbendjele BaYaka) (Akpanyung *et al*., 2013; Ariwaodo *et al*., 2012; Burkill, 1997; Etuk *et al*., 2020; Idu *et al*., 2009; Ihinmikaiye *et al*., 2021; Komlaga *et al*., 2015; Kpadehyea *et al*., 2022; Malan and Neuba, 2011; Salali *et al*., 2016; Uzodimma, 2013).

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All parts of the studied species, including roots, leaves, stems, fruits, and whole plants, are used by locals for traditional medicinal purposes, including erectile dysfunction and infertility, malaria, skin and intestinal infections, pains, diabetes, diarrhea, and tumors. Their extensive ethnomedicinal utility could be due to their exceptional pharmacological activities, which include antimicrobial, antioxidant, antisickling, analgesic, aphrodisiac, antistress, analgesic, and antimalarial (Bouquet and Debray, 1974; Egunyomi *et al.*, 2009, Okany *et al.*, 2012; Roumy *et al.*, 2008; Zamblé *et al.*, 2006a, 2006b). Medicinal plants' recent global acceptance and popularity due to their safe, low cost, easy accessibility, and effectiveness (Ogunmefun, 2018; Sofowora *et al.*, 2013) makes *M. keayana* and *M. puberula* potential source of bioactive compounds for drug discovery. Although some *in vitro* and *in vivo* pharmacological studies of the plants have been reported by several researchers, there is a need for more pharmacologic and clinical studies to prove its efficacy and safety, and support its use in traditional medicine.

Microdesmis keayana and *M. puberula* share several similarities ranging from their ethnobotanical description, distribution, uses, and phytochemical constituents (Dounias, 2008; Roumy *et al.*, 2008). An ethnobotanical survey in Southwestern Nigeria carried out at the early stage of this research revealed that the local names, "Idi-apata" and "Aringo" in Yoruba, are used mutually for both species among many traditional medicine practitioners and botanists and, thus, informed the need to report both species in this review article.

The present review is aimed to offer a firsthand compilation and databank of ethnopharmacology, phytochemistry, and biological activities of the plants, creating quick access information for future research on the plants.

METHODOLOGY

Relevant literature in this review was accessed from several electronic bibliographic databases, which include PubMed, Medline, Google, Google Scholar, Research Gate, Royal Botanical Garden Kew, JSTOR, The Plant List, and Academia, using several search terms, such as Microdesmis, M. puberula, M. keayana, chemical constituents, and ethnopharmacology of Microdesmis species. The search terms yielded more than 100 publications accessible online. The scientific names of the plants were validated using Royal Botanical Garden Kew, JSTOR, and The Plant List online websites.

Botanical description and distribution of *M. keayana* and *M. puberula*

Both *Microdesmis* species are nearly similar in morphology, making their identification difficult (Fig. 1). (Dounias, 2008). The two species are either short trees or shrubs that are dioecious, growing up to 6 m in height, with stems measuring up to about 8 cm in diameter. Their leaves are alternate and simple with about 4 mm long stipules. The petioles are generally 4–12 mm long with elliptical-oblong or ovate blades and asymmetrical bases looking cuneate to round with an acute and somewhat acuminate apex and finely toothed margin that is almost entire. Flowers are unisexual with green, short-hairy calyx, petals that are pink-orange, nearly circular to ovate-oblong, and short-hairy in the upper half; female flowers have superior ovaries. Fruits of both species are ovoid drupe-shaped, measuring 10–12 × 9–11 mm. They are usually smooth when fresh but appear wrinkled when hard and appear shiny and red (one to two seeded). Seeds are primarily ovate, compacted, and rounded seedlings with epigeal growth (Alvarez Crus, 2008; Baker, 1913; Burkill, 1997; Schmeizer and Gurib-Fakim, 2008; van Welzen, 2011) (Fig. 1).

Microdesmis keayana and *M. puberula* are small woody trees found in temperate regions of Africa (Fig. 2). They are the most widely distributed among the nine species in the genus *Microdesmis* found in Africa (Royal Botanical Garden Kew, 2022; van Welzen, 2011) (Fig. 2).

ETHNOMEDICINAL USES

Generally, almost all parts of *M. keayana* and *M. puberula,* such as fruits, leaves, leaf twigs, stem bark, root, and whole plants, are used for ethnomedicinal purposes. The plants have a vast range of traditional medicinal applications that include preparations, such as decoctions and paste for treating erectile dysfunction, pains, wound healing, and infections, respectively. *Microdesmis puberula* is used as a browse plant for cattle and goats (Esonu *et al.*, 2004; Okon *et al.*, 2017). The traditional use of the plants, their local names, and methods of preparation are shown summarized in Table 1.

CHEMICAL CONSTITUENTS

Previous investigations on *Microdesmis* species revealed the presence of polyamine alkaloids, such as spermine and spermidine derivatives as well as quinolones in *M. keayana* and *M. puberula* (Roumy *et al.*, 2008; Zamblé *et al.*, 2006a, 2006b). The leaves and roots were reported to possess important phytochemicals, such as alkaloids, flavonoids, saponins, steroids, tannins, and terpenoids (Akpanyung *et al.*, 2013; Gbadamosi and Oloyede, 2014; Odesanmi *et al.*, 2012; Okon *et al.*, 2017). Coumarins and anthraquinones were found to be present in the roots and leaves of *M. keayana* by Acheampong *et al.* (2018), while Akpanyung *et al.* (2013) found reducing sugars in the roots of the plant. Studies to evaluate the nutritional and quantitative phytochemical properties of *M. puberula* revealed that the leaf contained alkaloids, saponins, cardiac glycosides, terpenes, and nutrients like carbohydrates, crude proteins, minerals, e.g., zinc, iron, calcium, potassium, magnesium, and phosphate alongside with other vitamins (A, B1, B2, and C) (Esonu *et al.*, 2004; Okon *et al.*, 2018; Umoh *et al.*, 2004; Uwemedimo *et al.*, 2018). Studies by Abakedi and Asuquo (2016), Abakedi (2017), and Abakedi and Sunday (2021) revealed that *M. puberula* leaf and root extracts inhibited the corrosion of aluminum in an acidic medium, which was predicted to be due to the presence of heteroatoms like nitrogen, oxygen, and sulfur in alkaloids, terpenes, and anthraquinones.

Figure 1. Pictures of *M. keayana* (A) West African Plants (2023) and *M. puberula* (B1-2) Flora of the World (2015).

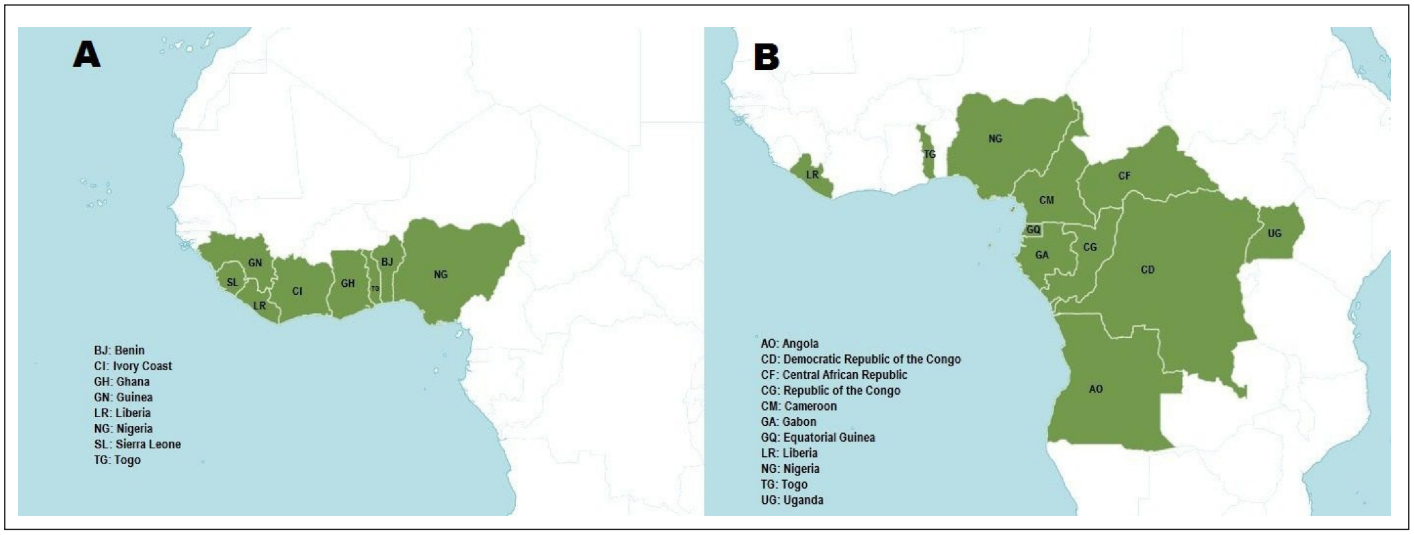

Figure 2. Map showing the geographical distribution of M. keayana (A) and M. puberula (B) (Royal Botanical Garden Kew).

Three spermidine alkaloids were isolated from the methanol root extract of *M. keayana* by Zamble *et al*. (2006a, 2006b); N^5, N^{10}-di(p-coumaroyl)-N^1-feruloylspermidine (Keayanidine A)**(1)**, N^5-(p-coumaroyl)-N^1, N^{10}-diferulosylspermidine (Keayanidine B)**(2)**, and N^1, N^5, N^{10}-triferuloylspermidine (Keayanidine C)**(3)**. In another study by Zamble *et al*. (2007) on the hydromethanolic root extract of *M. keayana*, two new compounds: xanthoquininamide (6-hydroxyquinoline-4-carboxamide) **(4)** and N^5-(p-coumaroyl)-N^1, N^{14}-diferuloyl spermine (keayanine) **(5)** were isolated, the latter being a spermine derivative. In addition, Roumy *et al*. (2008) reported the isolation of three spermines: N^1, N^5, N^{15}-tris(p-coumaroyl) spermine (Keayanaine B) **(6)**, N^1-feruloyl-N^5, N^{15}-di(p-coumaroyl) spermine (keayanaine C) **(7),** and N^1, N^5, N^{15}-tris(feruloyl) spermine (keayanine D) **(8)** from the hydromethanolic extracts of *M. keayana* and *M. puberula* roots. Roumy *et al*. (2008), in the same study, isolated four compounds: keayanidines A, B, and C, and keayanine A (previously isolated in *M. keayana* root) from the root of *M. puberula*. The isolated chemical compounds with their structures and classes are summarized in Figure 3.

PHARMACOLOGICAL ACTIVITIES

The various pharmacological activities of *M. keayana* and *M. puberula* include aphrodisiac, antimicrobial, antioxidant, analgesic properties, antiplasmodial, and antistress activities. (Acheampong *et al*., 2018; Bawo *et al*., 2020; Cagri-Mehmetoglu *et al*., 2017; Okany *et al*., 2012; Vonthron-Sénécheau *et al*., 2003; Zamblé *et al*., 2006a, 2006b; 2008 and 2009) (Table 2). Previous studies on the plants revealed several overlaps in their pharmacological activities (Table 3).

Fertility and aphrodisiac properties

Plant products that have antioxidant and sexually potentiating properties can be used as treatment choices for infertility in males (Muanya and Odukoya, 2008; Zamblé *et al*., 2009). The effect of *M. keayana* aqueous root extract on vasorelaxant and hypotensive activity in normotensive rabbits and guinea pig aorta strips using the organ bath was investigated by Zamblé *et al*. (2006a, 2006b). It was revealed that *M. keayana* root increased endothelial nitric oxide synthetase 3 (eNos) messenger ribonucleic acid (mRNA) (an important enzyme that synthesizes nitric oxide (NO), an essential mediator of erectile function) levels and NO production and also reversed oxidative stress due to its antioxidant properties. The result showed a positive correlation in its sexual behavioral functions, which supports the use of *M. keayana* use in ethnomedicine for the management of erection problems. Several studies have shown the expression and increased activity of eNOS during erection, which results in increased NO production (Li *et al*., 2019; Wen *et al*., 2011). Zamblé *et al*. (2008) further studied the sexual behavioral actions of aqueous root extract and two compounds keayanidine B and keayanine isolated from *M. keayana*, on male albino rats. The aqueous extract and pure isolated alkaloids were administered orally at doses of 150 and 3 mg/kg, respectively, to male albino rats. *Microdesmis keayana* root extract significantly increased mounting frequency, decreased mount latency, and increased intromission and ejaculatory frequencies after 1 hour 15 minutes and 3 hour 15 minutes. Zamblé *et al*. (2009) in a study to explore the pharmacologic basis surrounding the ethnomedicinal use of *M. keayana* for treating erection dysfunction, evaluated two compounds keayanidine B and keayanine (from *M. keayana* root extract) for their potential to induce vasodilation in isolated aortic rings of rats. Keayanidine B and keayanine, administered in ranging concentrations of 1.10^{-9}–3.10^{-4} M, were found to cause a relaxed contraction induced by phenylephrine with IC_{50} of 23.3 ± 1.3 µM/l for keayanidine B and 27.5 ± 2.4 µM/l for keayanine in a dose-dependent fashion. The results showed that the vasodilating properties of the two isolated alkaloids were caused by their ability to increase eNos mRNA and NO levels.

Muanya and Odukoya (2008) investigated the fertility effect of *M. keayana* ethanol root extract and other plant root extracts commonly used in South West Nigeria for treating erectile dysfunction and boosting sperm count and libido in

Table 1. Ethnomedicinal uses of M. keayana and M. puberula.

Scientific name	Country/region	Plant part used	Ethnomedicinal recipe	Traditional use	Reference
M. keayana	Africa (general)	Leaves, twig, whole plant, root	Enema	Diarrhea	Schmeizer and Gurib-Fakim, 2008; Ramandeep *et al.,* 2012
			Decoction	Aphrodisiac	
	Sierra Leone	Leaves	Paste made from pounded leaves, white clay, and leaves of *Desmodium adscendens*	Scabies	Alvarez, 2008; Burkill, 1997, Schmeizer and Gurib-Fakim, 2008; Sofowora, 1982
		Leaves	Cooked with chicken	Palpitations	Alvarez, 2008; Burkill, 1997, Schmeizer and Gurib-Fakim, 2008
		Leaves	Liniment	Bone fracture	Alvarez, 2008; Burkill, 1997, Schmeizer and Gurib-Fakim, 2008
	Sierra Leone, Senegal, Ivory Coast and Nigeria	Leaves, root	Crushed or burnt	Snake bites	Alvarez, 2008; Schmeizer and Gurib-Fakim (2008); Lebbie and Turay (2017); Gnahore *et al.,* 2022
	Liberia	Leaves	Infusion	Induce menstruation, abortifacient	Alvarez, 2008; Burkill, 1997, Schmeizer and Gurib-Fakim, 2008
	Ivory Coast	Leaves	Crushed with leaves of *Mareya micrantha*	General body pain	Alvarez, 2008; Burkill, 1997, Schmeizer and Gurib-Fakim, 2008
		Leafy twigs	Medicinal wash	Prevention of dermatological, intestinal disorders and excessive weight gain in newborn	Alvarez, 2008; Schmeizer and Gurib-Fakim, 2008
		Leaves	Ground with Capsicum fruit or as a decoction	Fatigue, Pain, Fever	Alvarez, 2008; Schmeizer and Gurib-Fakim, 2008
		Leaves	Decoction	Rheumatism, migraine	Alvarez, 2008; Schmeizer and Gurib-Fakim, 2008
		Leaves	Sap	Epilepsy, convulsion	Schmeizer and Gurib-Fakim, 2008
		Bark, Leafy twigs, roots, whole plant	Ground macerate (applied as an enema), Infusion, Decoction	Aphrodisiac	Alvarez, 2008; Burkill, 1997, Schmeizer and Gurib-Fakim, 2008
		Leaves		Antidote to poison	Alvarez, 2008
		Leaves	Decoction	Migraine	Gnahore *et al.,* 2022
		Leaves	Decoction	Antidiabetic	Honoré *et al.,* 2020
		Leaves		Pregnancy (to maintain health)	Malan and Neuba, 2011
	Ghana	Bark, leafy twigs, roots, whole plant	Ground macerate (applied as an enema), Infusion, Decoction	Aphrodisiac	Alvarez, 2008; Burkill, 1997, Schmeizer and Gurib-Fakim, 2008
		Root	Decoction	Veneral diseases	Alvarez, 2008; Abbiw, 1990, Burkill, 1997, Schmeizer and Gurib-Fakim, 2008
		Leaves, stem bark	Pulp	Sprains	Alvarez, 2008; Ayensu *et al.* (1978); Schmeizer and Gurib-Fakim, 2008
		Fruit	Decoction	Tumor	Alvarez, 2008; Schmeizer and Gurib-Fakim, 2008
		Fruit	Chewed	Ulcer	Alvarez, 2008; Schmeizer and Gurib-Fakim, 2008
		Root bark	Concoction with leaves of *Piper guineensis*	Mastitis	Alvarez, 2008; Schmeizer and Gurib-Fakim, 2008
		Twigs	Chewing sticks	Oral health	Alvarez, 2008; Abbiw, 1990; Alvarez, 2008; Burkill, 1997; Schmeizer and Gurib-Fakim, 2008
	Togo	Leaves	Decoction with roots of *Newbouldia laevis* (orally and taken as a bath)	Mental disorder	Alvarez, 2008; Burkill, 1997, Schmeizer and Gurib-Fakim, 2008

Continued

Scientific name	Country/region	Plant part used	Ethnomedicinal recipe	Traditional use	Reference
M. puberula	Africa (general)	Root, leaves	Infusion	Infertility, aphrodisiac, menstrual problems, cough, provide strength, laxative, pterygium, warts	Ayensu *et al*. (1978); Carter and Radcliffe-Smith, 1988; Schmeizer and Gurib-Fakim, 2008; Ariwaodo *et al.,* 2012; Soladoye *et al.,* 2014; Herbpathy, 2015; Makinde *et al.,* 2015
		Stem bark	Crushing		
		seed	Crushing (mixed with Capsicum fruits)		
		fruits	whole		
	Nigeria	Bark	Decoction	Obesity	Ajayi and Moody, 2015; Makinde *et al.,* 2015
		Leaves	Decoction	Acute spleen pain	Burkill, 1997; Schmeizer and Gurib-Fakim, 2008
		Leaves, roots	Leaves are put in vapor baths	Rheumatism and Arthritis	Okafor and Ham, 1999; Schmeizer and Gurib-Fakim, 2008; Ogunmefun and Gbile, 2012; Gbadamosi and Oloyede, 2014; Muanya, 2018
		Twigs	Chewing sticks	Oral health	Idu *et al.,* 2009
		Stem bark		Fetus development	Kayode and Akinluyi, 2016
		Stem	Decoction	Epilepsy	Wahab, 2015
	Ivory Coast	Leaves, twigs, roots	Crushing	Antivenom	Ayensu *et al.,* 1978; Burkill, 1997; Ncube *et al.*, 2008; Schmeizer and Gurib-Fakim, 2008
		Leaves	Wash the head with macerated leave	Severe headache	Schmeizer and Gurib-Fakim, 2008
	Cameroon, Ivory Coast, Ghana Nigeria, and Liberia	Leaves, twigs	Enema	Diarrhea and Intestinal problems	Bouquet and Debray, 1974; Ayensu *et al.* (1978); Schmeizer and Gurib-Fakim, 2008; Ariwaodo *et al.,* 2012; Ajayi and Moody, 2015; Kpadehyea *et al.,* 2015; Agyarea *et al.,* 2018; Lawal, *et al.,* 2022
		Fruits	Crushing (mixed with capsicum fruits)	cough	Schmeizer and Gurib-Fakim, 2008; Betti, 2004
		Leaf sap	Nose drops	Malaria and cough	Schmeizer and Gurib-Fakim, 2008
			Eye drop	Blurred vision	
	Ghana	Stem	Paste from ashes of burnt stem mixed with palm oil	To prevent limping in infants	Ayensu *et al.,* 1978; Schmeizer and Gurib-Fakim, 2008
		Leaves	Paste	Relieve backache	Ayensu *et al.,* 1978; Schmeizer and Gurib-Fakim, 2008
	Ghana and Nigeria	Fruits	Decoction	Tumors	Agyarea *et al.*, 2018; Hartwell, 1967
				Tumor (breast and prostate)	
		Leaves	Decoction	Malaria	Komlage *et al.,* 2015
	Ghana, Nigeria and Liberia	Leaves, stem bark	Infusion	Skin problems (boils) and wound	Neuwinger, 2000; Schmeizer and Gurib-Fakim, 2008; Ariwaodo *et al.,* 2012
	Central African Republic	Leaves		Ease of delivery in pregnancy	Schmeizer and Gurib-Fakim, 2008; Lawal *et al.,* 2022
		Leaves	Decoction	Mastitis	Schmeizer and Gurib-Fakim, 2008
		Leaves	Crushing	To strengthen the bones of infants	Schmeizer and Gurib-Fakim, 2008
	Gabon	Leaves	Wash the head with macerated leave	Severe headache	Schmeizer and Gurib-Fakim, 2008
		Bark	Decoction	Diabetes-mellitus	Tjeck *et al.,* 2017
		Aerial parts	-	Opportunistic Infection in HIV	Boukandou, 2019

Continued

Scientific name	Country/region	Plant part used	Ethnomedicinal recipe	Traditional use	Reference
	Republic of Congo	Leaves	Decoction	Prevent fainting	Schmeizer and Gurib-Fakim, 2008
		Leaves	Whole	Sore throat and colds	Schmeizer and Gurib-Fakim, 2008
		Leaves	Ear drop	Ear infections	Dounias, 2008; Schmeizer and Gurib-Fakim, 2008
	DR Congo and Republic of Congo, Nigeria	Leaves	Crushed leaves mixed with leaves of several plants	Fever	Betti, 2004; Schmeizer and Gurib-Fakim, 2008; Uzodimma, 2013
		Bark and wood	Paste from ashes of burnt bark	Rib pain	Betti, 2004, Schmeizer and Gurib-Fakim, 2008
		Stem bark	Crushing	Pneumonia	Dounias, 2008; Schmeizer and Gurib-Fakim, 2008
	Burundi, Nigeria and Rwanda	Roots	Crushing	Gonorrhoea	Schmeizer and Gurib-Fakim, 2008; Ajibesin *et al.*, 2008

males. Lipid peroxidation was used as an index to evaluate the aphrodisiac properties of these plants. The lipid peroxidation activity of the plants was assayed by measuring malondialdehyde levels in the homogenate of raw and cooked fish. The findings indicated that *M. keayana* root extract significantly decreased lipid peroxidation due to its antioxidant properties (Muanya and Odukoya, 2008).

The aphrodisiac potential of the two *Microdesmis* species needs more exploration as some commercial herbal products in the market have *M. keayana* as one of the ingredients (Barlowesherbalelixirs, 2020). The evidence above supports the use of *M. keayana* as an aphrodisiac in folklore. However, no scientific discoveries existed to support the traditional use of *M. puberula* as an aphrodisiac or fertility enhancer. This scientific gap indicates the need for more pharmacological research on both plants, especially on fractions and isolated compounds.

Antimalarial activities

Malaria is an endemic disease that affects more than 3.5 billion people worldwide, with higher mortality rates in Africa (Snow and Omumbo, *et al*., 2006). It is transmitted by *Plasmodium* sp. majorly *Plasmodium falciparum* (Bawo *et al*., 2020; WHO, 2022). *Microdesmis keayana* is used traditionally for treating malaria. This ethnomedicinal claim was confirmed when the antiplasmodial and cytotoxic activity of *M. keayana* methylene chloride leaves extract was evaluated alongside three Ivorian plants (Vonthron-Sénécheau *et al*., 2003). Four of the extracts were tested on K1 chloroquine-resistant *P. falciparum* strain by *in vitro* microculture radioisotope technique, which uses the uptake of [^{3}H]hypoxanthine by parasites as an indicator of viability. The results showed that *M. keayana* methylene chloride and methanol leaf extract were able to inhibit *P. falciparum* growth by inhibiting the uptake of [^{3}H]hypoxanthine with IC_{50} values of 12.2 µg/ml and >20 µg/ml for methylene chloride and methanol extracts, respectively (Vonthron-Sénécheau *et al*., 2003). Zirihi *et al*. (2005) studied the antiplasmodial and cytotoxicity of *M. keayana* ethanol root extract and 32 other West African plants against the chloroquine-resistant FcB1/Colombia strain of *P. falciparum* by *in vitro* models. The finding showed *M. keayana* extract was inactive against *P. falciparum* with IC_{50} values >50 g/ml. The larvicidal activity of *M. puberula* hexane leaf extracts, along with two other plants, was evaluated using biolarvicidal bioassay protocols, and Dipex pesticide (1 ppm) was used as a positive control (Bawo *et al*., 2020). The result showed a significant increase in the mortality rate of mosquito larvae, with the highest and lowest mortality rate at 70 and 10 ppm, respectively. Similarly, the hexane leaf extracts also had a biolarvicidal effect at an LC_{50} value of 32.83 ppm.

The report above shows some disparity in the *in vitro* antiplasmodial results of *M. keayana*. This necessitates the need for more scientific investigation on other solvent fractions and pharmacological screening techniques to validate the traditional usage of plants in curing malaria. Also, further research is encouraged on the isolation of bioactive compounds with antiplasmodial activity as a scaffold for new drug development for malaria treatment and to better understand the mechanism of action.

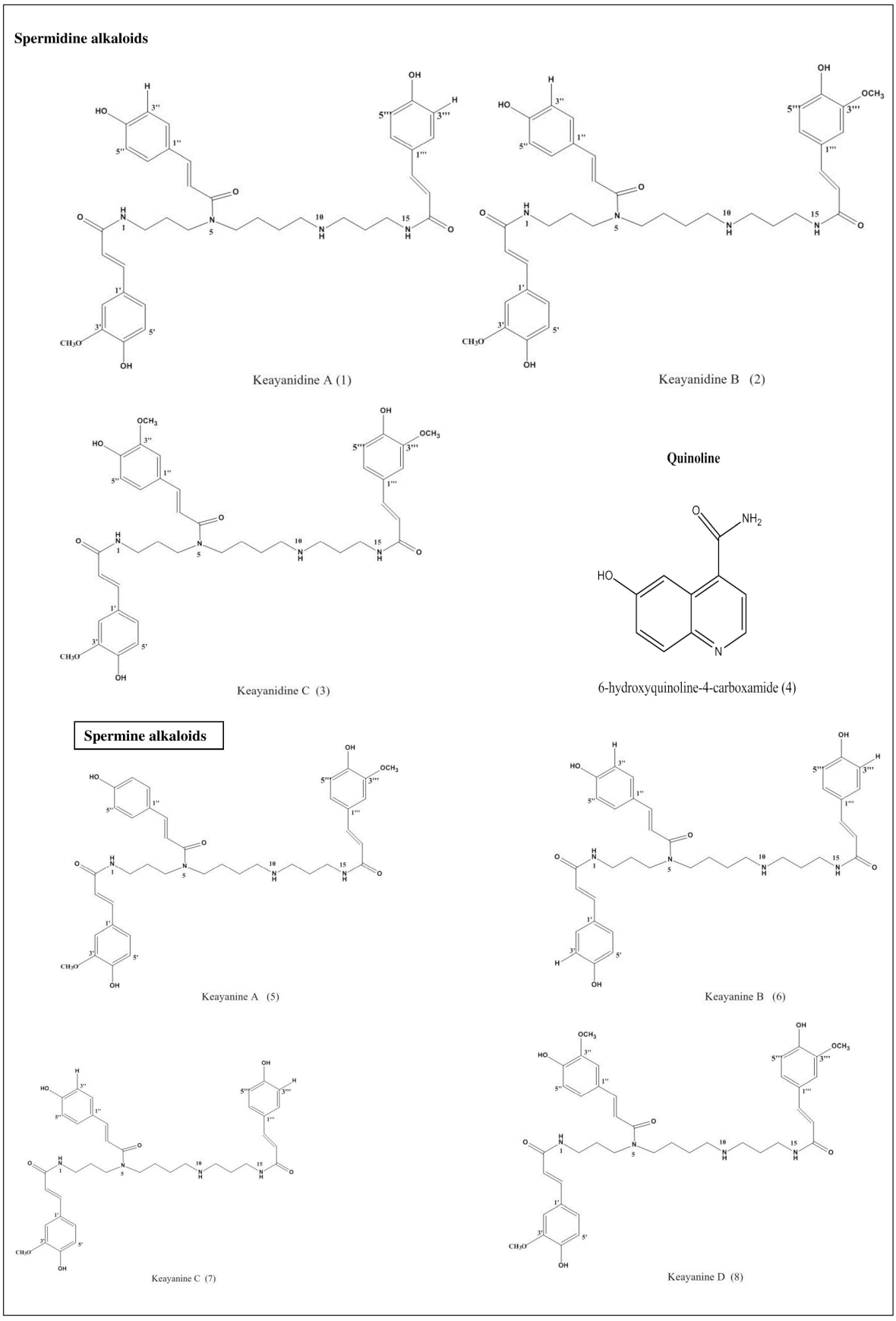

Figure 3. Chemical structures and names of compounds reported from *M. keayana* and *M. puberula.*

Table 2. Pharmacological activities of *M. keayana* and *M. puberula*.

Pharmacological activities	Scientific name	Part used	Extract/fraction	Model	Dosage/duration	Type of pharmacological effect	References
Aphrodisiac and fertility properties	*Microdesmis keayana*	Root	Aqueous extract	*In vitro*	(50, 500, 750, and 5,000 g/ml) (0 to 200 g/ml)	Vasoactivity and antioxidant properties	Zamblé *et al.*, 2006, 2006b
					150 mg/kg/3 mg/kg	Sexual behavior	
		Root	Aqueous extract/ keayanidine B and keayanine isolated from the methanol and hydromethanolic root extracts	*In vivo*			Zamblé *et al.*, 2008
		Root	Keayanidine B and keayanine isolated from the methanol and hydromethanolic root extracts Ethanol (50%)	*In vitro*	(1.10^{-9}–3.10^{-4} M)	Vasodilating and antioxidant properties	Zamblé *et al*., 2009
						Reduced lipid peroxidation and aphrodisiac effect	
		Root		*In vitro*			Muanya *et al*., 2008
Antimalarial and biolarvicidal activities	*Microdesmis keayana*	Leaves	Methylene chloride extract	*In vitro*	0.47–30 µg/ml	Antiplasmodial and cytotoxic activity	Vonthron-Senecheau *et al*., 2003
							Bawo *et al*., 2020
	Microdesmis puberula	Leaves	n-Hexane extract	*In vitro*	0–70 ppm	Biolavicidal activity	
		Leaves	Ethanol	*In vitro*	Diluted conc. from a stock of 10 mg/ml	Antiplasmodial and cytotoxic activity	Zirihi *et al*., 2005
Antimicrobial activities	*Microdesmis puberula*	Stem bark	Methanol and petroleum ether extract	*In vitro*	5%, 10%, 15%, and 20%	Antimicrobial activity	Acheampong *et al*., 2018
		Leaves		*In vitro*	0.5–25 mg/l	Antibacterial activity	Cagri-mehmetoglu *et al*., 2017
Antioxidant activity	*Microdesmis puberula*	Stem bark	Methanol and petroleum ether extracts	*In vitro*	200, 100, 50, 25, 12.5, 6.25, 3.125, and 1.56 µg/ml	Antioxidant activity	Acheampong *et al.*, 2018
	Microdesmis keayana	Root	Aqueous	*In vitro*		Antioxidant activity	Zamblé *et al*., 2006, 2006b
		Root	Keayanidine B and keayanine isolated from the methanol and hydromethanolic root extracts	*In vitro*		Antioxidant activity	Zamblé *et al.*, 2009

Continued

Pharmacological activities	Scientific name	Part used	Extract/fraction	Model	Dosage/duration	Type of pharmacological effect	References
Analgesic activity	*Microdesmis puberula*	Stem	Methanol extract	*In vivo*	600–2,400 mg/kg	Analgesic property	Okany *et al.*, (2012)
		Stem wood	Methanol extract	*In vitro*	600 mg/kg	Antiulcer and antistress property	Okany *et al*., (2012)
Antisickling activity	*Microdesmis puberula*	Root	Herbal recipe	*In vitro*	0.5 ml	Antisickling property	Egunyomi *et al*., (2009)
Toxicity study	*Microdesmis puberula*	Root	Ethanol extract	*In vivo*	200, 400 and 600 mg/kg	Biochemical and hematological parameters	Akpanyung *et al*., (2013)

Table 3. Summary of the similarities and differences between *M. keayana* and *M. puberula*.

S/N	Description	*Microdesmis keayana*	*Microdesmis puberula*	References
1.	**Taxonomy**			
	Name	*Microdesmis keayana*	*Microdesmis puberula*	Burkill, 1997; Alvarez Crus, 2008; Etuk *et al*., 2020; Idu *et al*., 2009; Malan and Neuba, 2011; Ariwaodo *et al.*, 2012; Akpanyung *et al.*, 2013; Uzodimma, 2013; Komlaga *et al*., 2015; Salali *et al*., 2016; Ihinmikaiye *et al*., 2021; Kpadehyea *et al.*, 2022.
	Author	J.Leonard	Hook.f. ex Planch.	
	Family	Pandaceae	Pandaceae	
	Local names	Sonoufoko, Idi-apata, Aringo, Igi-ope, Mkpiri, Kpirimbo, Amama, Erankpata, Ntanebit, Akpalata, Ingolongolo, Kawa, Babében evela, Gbihi, Kondgu, Kpendeile, Bulon, Efima	Sonoufoko, Esunsun, Idi-apata, Aringo, Igi-ope, Igi ori apata, Mkpiri, Mbugbo, Kpirimbo, Amama, Erankpata, Ntanebit, Akpalata, Ingolongolo, Ofema, Nikee, Dikota, Mokula	
2.	**Botanical features**			
	Description	Short dioecious shrubs, 6 m in height, and about 8 cm in diameter	Short dioecious shrubs, 6 m in height, and about 8 cm in diameter	Baker, 1913; Burkill, 1997; Alvarez Crus, 2008; Schmeizer and Gurib-Fakim, 2008; van Welzen, 2011
	Geographical distribution	Benin, Ivory Coast, Ghana, Guinea, Liberia, Nigeria, Sierra Leone, and Togo	Angola, DR Congo, Central African Republic, Republic of the Congo, Cameroon, Gabon, Equatorial Guinea, Liberia, Nigeria, Togo, and Uganda	van Welzen, 2011; Royal Botanical Garden Kew, 2022
3.	**Ethnobotany**			
	Traditional uses	Infertility, aphrodisiac, pains, fever, wound healing, diarrhea, snake bites abortifacient, menstrual problems, tumors, ulcer malaria, cough, and obesity, antidiabetic, and skin disorders	Infertility, aphrodisiac, pains, fever, severe headache, wound healing, snake bites, ease delivery in pregnancy, tumors, ulcer, malaria, cough, laxative, intestinal problems, epilepsy, gonorrhea, ear infections, and obesity	Alvarez Crus, 2008; Burkill, 1997, Schmeizer and Gurib-Fakim, 2008
	Parts used	Leaves, roots, stem bark, and twigs	Leaves, roots, stem bark, and twigs	
4.	**Pharmacognostic features**	-	Epidermal cell: arched; stomatal type: anomocytic	Obemebe, 2015
5.	**Phytochemical constituents**	Alkaloids (spermine and spermidine derivatives), flavonoids, saponins, steroids, tannins, and terpenoids, coumarins, anthraquinones	Alkaloids (spermine and spermidine derivatives), flavonoids, saponins, steroids, tannins, and terpenoids, terpenes, and nutrients like carbohydrates, crude proteins, minerals	Zamblé *et al*., 2006a, 2006b; Roumy *et al.*, 2008; Odesanmi *et al*., 2012; Akpanyung *et al*., 2013; Gbadamosi and Oloyede, 2014; Okon *et al*., 2017; Acheampong *et al*., 2018
6.	**Pharmacological studies**	Fertility and aphrodisiac activities	Antimalarial activity	Zamblé *et al*., 2006a, 2006b, 2008, and 2009; Acheampong *et al*., 2018; Bawo *et al.*, 2020; Cagri-Mehmetoglu *et al*., 2017; Okany *et al*., 2012; Vonthron-Sénécheau *et al*., 2003
		Antimalarial activity	Antimicrobial activity	
		Antimicrobial activity	Antioxidant activity	
		Antioxidant activity	Analgesic and antistress properties	
		Antisickling activity	Toxicity studies	
		Toxicity studies		

Antimicrobial activity

Acheampong *et al*. (2018) assessed the antimicrobial activity of methanol and petroleum ether stem extracts of *M. puberula* by the agar diffusion method against designated microorganisms were used, such as *Salmonella typhi, Bacillus subtilis, Pseudomonas aeruginosa, Candida albicans, Klebsiella pneumonia, Streptococcus pyogenes, Enterococcus faecalis, Staphylococcus aureus, Neisseria gonorrhoeae, and Escherichia coli*. The methanol extract inhibited the growth of Gram-positive and Gram-negative bacteria in the agar diffusion test at 12–16 ppm, while the petroleum ether extract exhibited no antimicrobial activity, both having minimum inhibitory concentration value of 6.25–12.5 and 50–200 mg/ml, respectively. Also, the antibacterial properties of *M. puberula* leaf extract and three other medicinal plants in Nigeria (*Hypoestes verticillaris, Icacina trichantha,* and *Enterolobium cyclocarpum*) were evaluated by Cagri-Mehmetoglu *et al*. (2017). *Microdesmis puberula* extract inhibited the growth of *S. aureus* and *E. sakkai* with an inhibition zone of 8 mm.

The use of *M. keayana* and *M. puberula* in treating infections and skin diseases in ethnomedicine is yet to be extensively proven scientifically. The above report shows they are active against designated microorganisms. Possible isolation of bioactive lead compounds with antibacterial and antifungal activities is vital and encouraged.

Antioxidant activity

Antioxidants are important defense mechanisms of the body against the deleterious effect of free radicals, such as reactive oxygen species, involved in the development of several disease conditions (Agarwal and Prabakaran, 2005). Previous studies have shown that *M. keayana* and *M. puberula* are natural antioxidant reservoirs (Acheampong *et al*., 2018, Zamblé *et al*., 2006a, 2006b). Acheampong *et al*. (2018) investigated the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging properties and total antioxidant capacity of *M. puberula* methanol and petroleum ether stem bark extracts. The results showed both extracts possess DPPH radical scavenging activity with IC_{50} values of 1.1 and 1.2 µg/ml, respectively. The methanol extract proved more potent than the petroleum ether extract with a total antioxidant capacity of 21.75 mg ascorbic acid equivalent/gram of dry extract and 96.11 mg ascorbic acid equivalent/gram of dry extract for petroleum ether at the lowest extract concentration of 1.56 µg/ml. Studies by Zamblé *et al*. (2006a, 2006b) on the antioxidant activity of *M. keayana* aqueous root extract on superoxide anion, hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), and hydroxyl radical (HO•) revealed that the extract had a very significant dose-dependent radical scavenging activities in two systems (cellular and noncellular) against superoxide radical-anion with IC_{50} of 34.29 ± 2.384 and 19.46 ± 1.90 g/ml for noncellular and cellular systems, respectively. It also showed substantial scavenging activities against H_2O_2, HO•, and HOCl with IC_{50} of 49.75 ± 0.25, 57.8 ± 0.75, and 63.5 ± 0.5 g/ml, respectively (Zamblé *et al*., 2006a, 2006b). In another study, Zamblé *et al*. (2009) investigated DPPH radical scavenging, $O_2^{\bullet-}$, and H_2O_2 antioxidant activity of keayanidine B and keayanine isolated from the root of *M. keayana*. Keayanidine B and keayanine showed strong antioxidant effects against DPPH with IC_{50} values of 33.0 ± 0.7 and 30.2 ± 0.9 µM/l, respectively, and against superoxide anion and H_2O_2 with IC_{50} varying from 16.2 ± 0.4 to 20.2 ± 0.7 µM/l in the cell-free system and from 13.2 ± 0.7 to 16.3 ± 0.8 µM/l in the cellular system (Zamblé *et al*., 2009). The antioxidant activities of the root and stem bark extracts of *M. keayana* and *M. puberula* could be responsible for the pharmacological activity of the plants, which further gives credence to their use in folklore as fertility enhancers, aphrodisiacs and in the treatment of other disease conditions triggered by reactive oxygen species (Zamblé *et al*., 2006a, 2006b and 2009). Further research is crucial to isolate antioxidant phytochemicals from the various parts of the plants.

Analgesic and antistress properties

Microdesmis keayana and *M. puberula* are used in ethnomedicine as pain relievers (Alvarez Crus, 2008; Ayensu, 1978; Betti, 2004; Muanya, 2018; Schmeizer and Gurib-Fakim, 2008). The analgesic property of *M. puberula* methanol stem wood extract was investigated by Okany *et al*. (2012) using standard analgesic models like the acetic acid writhing and the hot plate analgesic tests. It was revealed that the extract significantly ameliorated both neurogenic and inflammatory pain dose-dependently at 600–2,400 mg/kg. Okany *et al*. (2012) employed the forced swimming test and immobilization stress-induced ulcer protocol to evaluate the antistress properties of *M. puberula* methanol stem wood extract. The results showed that the duration of immobility was significantly decreased by the extract at the dose of 600 mg/kg and also a reduced ulcer index in the stressed rats' group treated with the extract.

Antisickling activity

The antisickling activities of two herbal recipes were evaluated by Egunyomi *et al*. (2009). The first recipe consisted of *M. keayana* methanol root extract and 27 other plants, while the second recipe consisted of seven plant extracts without *M. keayana*, p-hydroxybenzoic acid, and normal saline were used as controls. The two herbal recipes demonstrated antisickling activity against sickled erythrocytes. The first ethnobotanical recipe containing *M. keayana* inhibited red blood cell (RBC) sickling with 63.4% inhibition, while the second herbal recipe had a percentage inhibition of 78.2% at 180 minutes incubation (Egunyomi *et al*., 2009). More scientific work is required to validate the antisickling property of the plant and the possible isolation of bioactive compounds as new agents against sickle cell disease.

Toxicity studies

Investigations of the acute toxicity profile of *M. keayana* and *M. puberula* were carried out in several toxicity studies to determine the safety of extracts of both plants. Okany *et al*. (2012) revealed that *M. puberula* has a safety profile of 15 g/kg when administered orally with an LD_{50} of 1,412.5 mg/kg. An acute toxicity study of *M. puberula* by oral administration on albino rats for 14 days revealed that the plant has a wide safety margin with an LD_{50} of more than 5,000 mg/kg (Akpanyung *et al*., 2013). Aspartate transaminase and alanine transferase levels of rats in the treatment groups were reduced when compared with the control group. No toxic effect on the liver and kidney was obtained, and hematological parameters like packed cell volume, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, and RBC were not significantly elevated. In contrast, the serum lipid profile

of *low-density lipoprotein* and triglycerides were significantly elevated with reduced high-density lipoprotein levels. Uwemedimo *et al*. (2018) investigated the acute toxicity of the leaf extract of *M. puberula* using albino mice by intraperitoneal (i.p.) route using the method of Lorke. The mean lethal dose (LD_{50}) of the extract was estimated to be 2,872.28 mg/kg, which proposes that ingestion as a leaf meal may not be detrimental to livestock and humans. *Microdesmis keayana* aqueous root extract following oral administration caused no death or toxicity at a dose of 2 g/kg body weight in albino rats (Zamblé *et al*., 2008). Acute and subacute toxicity studies on *M. keayana* and *M. puberula* have shown substantial safety and acceptability on all investigated parameters, supporting their widespread use in ethnomedicine.

CONCLUSION

This review, for the first time, has provided a compendium of information on the ethnopharmacological and phytochemical properties of *M. keayana* and *M. puberula*. The plants possess an untapped reservoir of phytochemicals as leads for drug discovery and development. There is a need for substantial studies for a proper understanding of the taxonomy and pharmacognostic similarities and differences of both species. The different plant parts, such as root, bark, and leaf, have close characteristics in terms of morphology, distribution, and overlapping medicinal uses. Some biological activities reported on *M. keayana* include antimicrobial, toxicity, antioxidant, antisickling, analgesic, aphrodisiac, and antimalarial, whereas in *M. puberula,* they comprise antibacterial, toxicity, antioxidant, antistress, analgesic, and antimalarial activities have been reported. Despite the pharmacological studies reported for both *Microdesmis* species, several ethnomedicinal claims need scientific data for validation and a better understanding of their mechanism of pharmacological actions, especially at the molecular level. Phytochemical investigations on the two plants have yielded about eight chemical compounds, the majority belonging to the groups of spermine and spermidine alkaloids. Most of the studies on *M. keayana* and *M. puberula* were on crude extracts, which has created a gap for further research, particularly on the fractions and the isolated compounds. Clinical studies on both species are encouraged to establish the dose, efficacy, and safety of human subjects in managing disease conditions, as challenges such as dose and dosage optimization have continuously posed major drawbacks in herbal medicine use. Acute and subacute toxicity reports on both species revealed that they are safe and nontoxic, as higher doses of the extracts elicited no adverse effects in experimental animals.

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List of abbreviations: eNos, endothelial nitric oxide synthase; mRNA, messenger ribonucleic acid, RBC, red blood cell.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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This study does not involve experiments on animals or human subjects.

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