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Traditional uses, phytochemistry and pharmacological properties of African *Nauclea* species: A review

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Keywords: Genus *Nauclea*, *N. latifolia*, *N. diderrichii*, *N. pobeguinii*, traditional medicine, malaria, pain, digestive ailments, infection, phytochemistry, indoloquinolizidines

Abstract

Ethnopharmacological relevance: The genus *Nauclea* in Africa comprises seven species. Among them, *N. latifolia*, *N. diderrichii* and *N. pobeguinii* are widely used by local population as traditional remedies. Preparation of various parts of plants (e.g. roots, bark, leaves) are indicated by traditional healers for a wide range of diseases including malaria, pain, digestive ailments or metabolic diseases.

Materials and methods: A literature search was conducted on African species of the genus *Nauclea* using scientific databases such as Google Scholar, Pubmed or SciFinder. Every

document of ethnopharmacological, phytochemical or pharmacological relevance and written in English or French were analyzed.

Results and discussion: The *Nauclea* genus is used as ethnomedicine all along sub-Saharan Africa. Several local populations consider *Nauclea* species as a major source of remedies for malaria. In this regard, two improved traditional medicines are currently under development using extracts from *N. latifolia* and *N. pobeguinii*. Regarding the chemical composition of the *Nauclea* genus, indoloquinolizidines could be considered as the major class of compounds as they are reported in every analysed *Nauclea* species, with numerous structures identified. Based on traditional indications a considerable amount of pharmacological studies were conducted to ensure activity and attempt to link them to the presence of particular compounds in plant extracts.

Conclusion: Many experimental studies using plant extracts of the African species of the genus *Nauclea* validate traditional indications (e.g. malaria and pain). However, bioactive compounds are rarely identified and therefore, there is a clear need for further evaluations as well as for toxicity experiments. The sustainability of these plants, especially of *N. diderrichii*, a threatened species, should be kept in mind to adapt local uses and preparation mode of traditional remedies.

1. Introduction

For centuries, medicinal plants of tropical sub-Saharan Africa have been extensively used by local communities for preparing traditional remedies, and still provide an important therapeutic option for a large part of the population (Moyo et al., 2015a). This fact is in line with the presence of higher number of traditional healers — 1 for 500 patients (WHO, 2013) — as compared with that of physicians — 1 for 6,700 patients (WHO, 2010) — in this region. Additionally, these practices are linked to one of the richest and most diverse ecosystems across

the world (Moyo et al., 2015b), with rain forests offering very specific environments that comprise 40% of plant species worldwide, whereas representing only 7–8% of the emerged land surface (Vlietinck et al., 2015). In aerial part arena, Rubiaceae is the largest family of woody plants with about 13,100 species spread in 611 genera in the wet tropics (Govaerts et al., 2013), where their known high alkaloid content correlates with an impressive body of reported past and present ethnopharmacological uses. The sub-Saharan traditional medicine indeed includes more than 60 Rubiaceae species for a wide portfolio of therapeutic indications, and these long-standing practices is still practiced to date (Karou et al., 2011).

From a botanical point of view, the Rubiaceae family is divided into three subfamilies (Rydin et al., 2009) including the Cinchonoideae with 220 species in 28 genera. It contains the tribe Naucleae with 17 genera (Löfstrand et al., 2014). This group can be easily distinguished from those of other tribe by its spherical inflorescences and its epigynous floral nectaries deeply embedded in the hypanthia (Verellen et al., 2007). It includes the genus *Nauclea* whose range is limited to the tropical areas of Africa and Asia. These trees have flattened terminal buds, and adpressed stipules deciduous or subsistent, ovate to elliptic. Their leaves are lustrous, green, opposite and pinnately nerved. Hypanthia and fruitlets can be free or connate into a syncarp. Flowers include corolla with imbricate lobes and fusiform stigma. Inflorescences contain 2-locular ovary with Y-shaped placentas (when they are attached to the upper third of the septum) or discoidal (when they are attached to the middle of the septum). Ovules are generally pendulous or spreading in all directions. Seeds are ovoidal to ellipsoidal and pitted (Löfstrand et al., 2014; Ridsdale, 1978). In Africa, the genus *Nauclea* contains seven species which can be distinguished by a combination of criteria (Figure 2), like their placentas, stipules shapes, and fruit type (Ridsdale, 1975), leaves shape, seeds margin and petiole length (Pellegrin, 1932), calyx and corolla pubescence, diameter of flowering heads, leaves pubescence (Ridsdale, 1978). *Nauclea latifolia* Smith, *Nauclea pobeguinii* (Hua ex Pobég.) Merr. and *Nauclea*

diderrichii (De Wild.) Merr. seem to be most widely distributed in an area that extends from the center to the west of tropical Africa whereas *Nauclea vanderguchtii* (De wild.) Petit., *Nauclea gilleti* (De Wild.) Merr. and *Nauclea xanthoxylon* (Chev.) Aubr. (Löfstrand et al., 2014), appear to be far less common taxa. The exception is *N. nyasica* which occurs in Tanzania, Mozambique and Malawi (Figure 3).

This genus is well represented in several pharmacopoeias from West Africa (e.g. Benin, Central African Republic, Senegal, Ivory Coast), especially through the emblematic species *Nauclea latifolia*, whose alkaloid content and biological activities have been reviewed recently (Boucherle et al., 2016). Ethnopharmacological uses of *Nauclea pobeguinii* and *Nauclea diderrichii* are also heavily documented whereas others species were largely left behind. Medicinal indications of these species often match the specific needs of the regional health context in their occurring area. Indeed, as viral diseases, respiratory infections, diarrheas and malaria are the leading causes of death in sub-Saharan Africa (WHO, 2014), *Nauclea*-based corresponding remedies have been developed by local population and numerous antiplasmodial, antimicrobial or antidiarrheal uses have been reported. Besides, these ethnopharmacological data are widely supported by validated biological activities from both extracts and phytochemicals. The very recent clinical development of two antimalarial phytomedicinal preparations from *N. latifolia* (NIPRD-AM1; Gamaniel, 2009) and *N. pobeguinii* (PR 259 CT1; Mesia et al., 2011, 2012a, 2012b) in Nigeria and Democratic Republic of Congo respectively, is a perfect illustration of the potential of confronting traditional uses with objective biological assays and phytochemical analyses. Additionally, the extraction of the synthetic analgesic tramadol from *N. latifolia* roots by Boumendjel et al. (2013), albeit still controversial, contributed to put the genus under the spotlights during the past few years (Kusari et al., 2014, 2016; Lecerf-Schmidt et al., 2015; Nature, 2013; Romek et al., 2015).

Therefore, the aim of this review is to document the present knowledge about the traditional medicinal uses, the phytochemical composition, and the validated pharmacological activities of the *Nauclea* members from sub-Saharan Africa, and to highlight potential high-value connections between all these research fields.

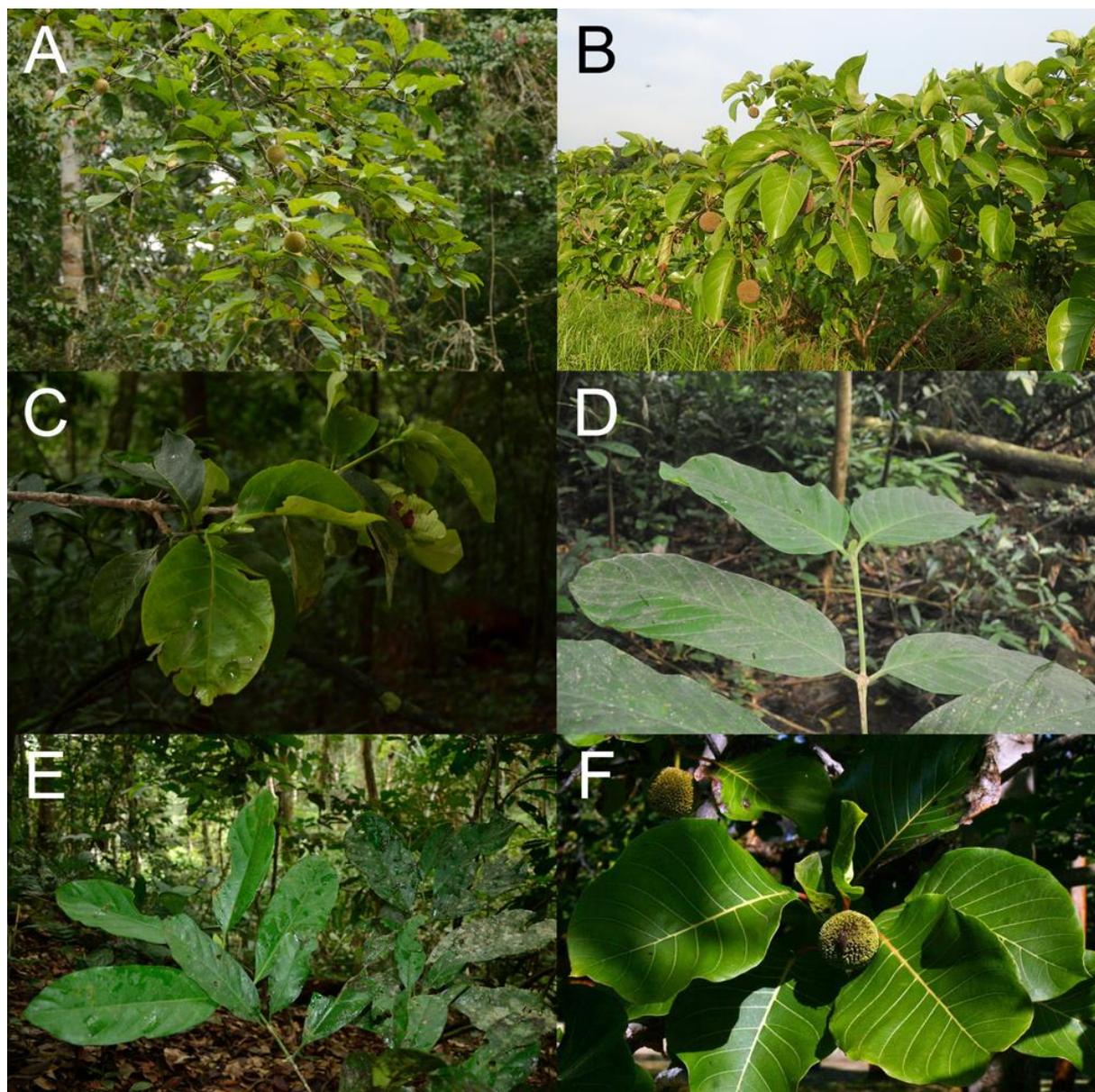


Figure 1. Photographs of six African *Nauclea* species. A. *N. pobeguinii* (Gabon, credit: Ehoarn Bidault). B. *N. latifolia* (Gabon, credit: Nicolas Texier). C. *N. diderrichii* (Guinea, credit: Ehoarn Bidault). D. *N. vanderguchtii* (unknown location, credit: David Kenfa). E. *N. gillettii* (Gabon, credit: Ehoarn Bidault). F. *N. nyasica*

(Zimbabwe, credit: Mark Hyde). The pictures are under Creative Commons licences (CC-BY-NC-ND or CC-BY-NC).

- 1- Ovaries and fruitlets free*Nauclea nyasica* (Hoyle) Å. Krüger & Löfstr.
[syn. *Burttdavya nyasica* Hoyle] Distribution: Tanzania to Mozambique3
- 2- Ovaries and fruitlets persistently connate into a syncarp3
- 3-
 - a. Stipules deltoid or short, obtuse, subpersistent. Placenta attached to the middle of the septum, somewhat discoidal, ovules spreading in all directions.....4
 - b. Stipules ovate, elliptic, or obovate, deciduous or subpersistent. Placenta attached to the upper third of the septum, y-shaped, ovules spreading in all directions but predominantly pendulous5
- 4-
 - a. Seeds pitted, ellipsoid non margined; leaves coriaceous, obtuse at base, petiole short, 1 to 2 cm long *Nauclea latifolia* Smith
[syn. *Sarcocephalus latifolius* (Sm.) E.A.Bruce, *Nauclea sambucina* T.Winterb., *Sarcocephalus esculentus* Afzel. ex Sabine, *Cephalina esculenta* (Afzel. ex Sabine) Schumach. & Thonn., *Sarcocephalus russegeri* Kotschy ex Schweinf., *Sarcocephalus sambucinus* K.Schum., *Nauclea esculenta* (Afzel. ex Sabine) Merr., *Sarcocephalus esculentus* var. *amarissima* A.Chev., *Sarcocephalus esculentus* var. *velutina* A.Chev.]
Distribution: W. Trop. Africa to Ethiopia and NW. Angola.
 - b. Seeds pitted, ellipsoids margined – leaves thin, attenuate, acute at base, petiole 4 to 5 cm long *Nauclea pobeguinii* (Hua ex Pobég.) Merr.
[syn. *Sarcocephalus pobeguinii* Hua ex Pobég.] Distribution: W. Trop. Africa to Zambia.
- 5-
 - a. Calyx lobes glabrous, sometimes sparsely hairy or ciliate; inside of calyx tube glabrous.....6
 - b. Calyx lobes mediumly to densely pubescent, inside of calyx tube pubescent*Nauclea diderrichii* (De Wild.) Merr.
[syn. *Sarcocephalus diderrichii* De Wild., *Sarcocephalus trillesii* Pierre ex De Wild., *Nauclea trillesii* (Pierre ex De Wild.) Merr., *Sarcocephalus badi* Aubrév.] Distribution: W. Trop. Africa to Uganda.
- 6-
 - a. Leaves pubescent below, at least on the veins*Nauclea xanthoxylon* (Chev.) Aubr.
[syn. *Sarcocephalus xanthoxylon* A.Chev.] Distribution: Ivory Coast to Sudan.
 - b. Leaves glabrous below.....7
- 7-
 - a. Diameter of flowering heads across corollas 40–60 mm, corolla lobes glabrous inside *Nauclea vanderguchtii* (De wild.) Petit.
[syn. *Sarcocephalus vanderguchtii* De Wild., *Sarcocephalus nervosus* Hutch. & Dalziel, *Sarcocephalus nervosus* var. *cordifolia* A.Chev.] Distribution: Liberia, Nigeria to WC. Trop. Africa.
 - b. Diameter of flowering heads across corollas up to 40 mm, corolla lobes with 1–3 lines of hairs inside*Nauclea gillettii* (De wild.) Merr.
[syn. *Sarcocephalus gillettii* De Wild., *Sarcocephalus trillesii* var. *lancifolia* A.Chev., *Nauclea lancifolia* (A.Chev.) Aubrév.] Distribution: Ivory Coast to WC. Trop. Africa.

Figure 2. Identification key of *Nauclea* species in Africa adapted from Ridsdale (1975, 1978) and Pellegrin (1932) with their distribution (Govaerts et al., 2013).

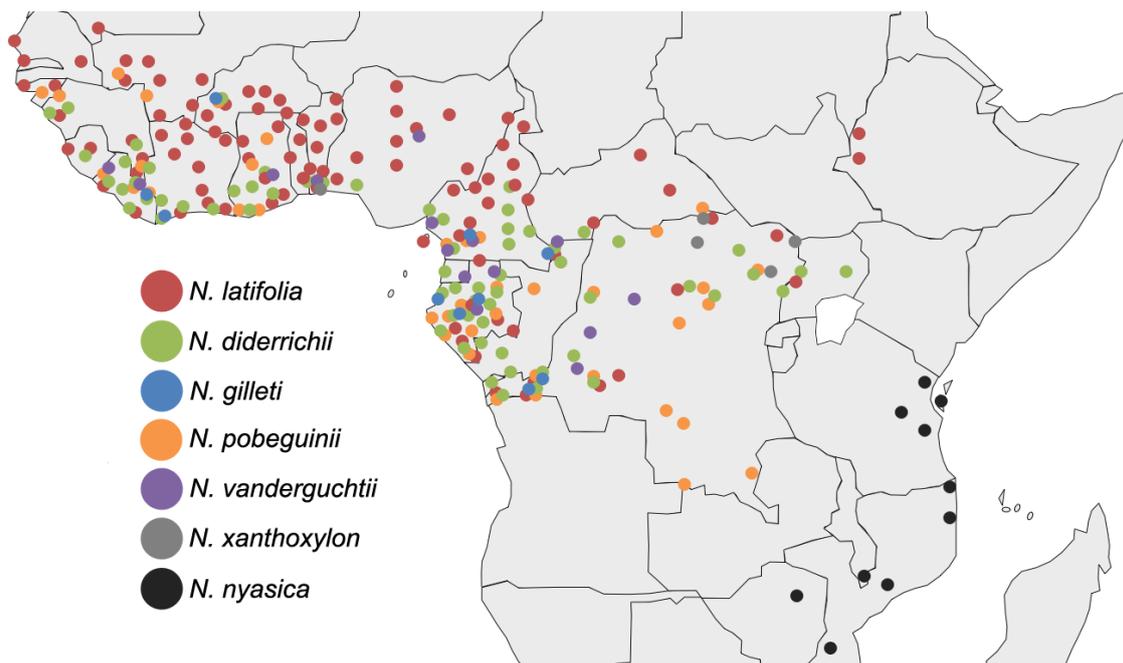


Figure 3. General geographical distribution of the seven African *Nauclea* species. The dots are compiled observations of specimens from various occurrence datasets (e.g. Naturalis Biodiversity Center, Tropicos Specimen Data, Herbarium of the “Muséum National d’Histoire Naturelle” of Paris, West African Vegetation Database) gathered by the Global Biodiversity Information Facility (<http://www.gbif.org>).

2. Non-medical ethnobotanical uses

Apart from therapeutic and healthcare considerations, some other ethnobotanical applications of African *Nauclea* species are described and reported in Table 1.

Table 1. Non-medical ethnobotanical uses of the genus *Nauclea* in sub-Saharan Africa

<i>Species</i>	<i>Plant parts</i>	<i>Uses</i>	<i>Reference</i>
<i>N. diderrichii</i>	W	Timber for building	Towns, 2014a
	B	Aphrodisiac	Towns, 2014a
	B	Bitter agent in place of hob for local beer fabrication	Desobgo et al., 2013
	Sd	Ground detoxification properties	Omorie et al., 2012

	S	Crafts and energy wood	Siribina et al., 2014
<i>N. latifolia</i>	S	Lumber and energy wood	Adeniyi, 2015
	F	Food for human, source of ascorbic acid	Ambé, 2001a; Ambé and Malaisse, 2001b
<i>N. pobeguinii</i>	F	Food for gorillas	Breuer, 2003
<i>N. vanderguchtii</i>	S	Timber and furniture	Obute and Ekiye, 2008
<i>N. xanthoxylon</i>	W	Lumber and energy wood	Dossou et al., 2012

Bark (B), Stem (S), Fruit (F), Seed (Sd), Wood (W).

Nauclea diderrichii wood is used as high-value primary material in building industries of West Africa, due to the high quality of timber (strength and durability) and its resistance to termites (Towns, 2014a). A survey conducted with 200 aboriginals showed the wide applications of *N. diderrichii* trunk for crafts, mortar for building housing, energy wood and canoe construction (Siribina et al., 2014). The bark is also used as an aphrodisiac (Towns, 2014a), and as a substitute for hops as bittering substance in the brewing of local beers (Desobgo et al., 2013). As a result, due to heavy exploitation and uncontrolled harvest (Jusu and Sanchez, 2014), *N. diderrichii* has been placed in 1998 on the IUCN Red List of Threatened Species, with a “vulnerable” status (IUCN, 2016). The plant also displays detoxifying property. Indeed, a recent research publication has described the ability of seeds to absorb the chromium (III) in aqueous solution (Omorie et al., 2012). This property is of particular interest, as *N. diderrichi* seeds are abundant and considered as waste in the plantations where the tree is produced as timber. Moreover, a study realized in the Apra Hills Forest Reserve in Ghana described the use of *N. latifolia* as primary materials for roofing and as heating source (Adeniyi, 2015). Similarly, *N. xanthoxylon* has been reported as energy wood and lumber for framework constructions in the swamp forest of Agonvè in Benin (Dossou et al., 2012). *N. vanderguchtii* was also described in Nigeria with applications for timber and furniture (Obute and Ekiye, 2008). Finally, the nutritional use of fruits of *Nauclea* species is reported. *N. latifolia* fruits, an excellent source of ascorbic acid, are for example used in Guinea by the Malinké ethnic group (Adeniyi, 2015). In

addition, a study on mammals conducted in Congo revealed that *N. pobeguinii* fruits are a feeding source for Gorillas (Breuer, 2003).

3. Ethnopharmacological uses

3.1. Anti-infective

3.1.1. Anti-malarial

As mentioned above, the recent clinical assays undertaken for two *Nauclea*-based antimalarial preparations in two different countries endorse a widespread traditional use of the genus in African communities against malaria. Indeed, the indication of *N. latifolia*, *N. diderrichii* and *N. pobeguunii* extracts have been often mentioned, sometimes with high citation frequency among the traditional healers (Table 2). The *Nauclea* genus especially appears among the most cited plants traditionally used for treating malaria in the Sélingué subdistrict of Mali (*N. latifolia*, 66% and *N. pobeguunii*, 55%; Diarra et al., 2015), in the Sierra Leone city Bo (*N. latifolia*, 50%; Ranasinghe et al., 2015), in the plateau of Allada in Benin (*N. latifolia*, 86% and *N. diderrichii*, 52%; Yetein et al., 2013), and in Southern Nigeria (*N. latifolia*, 46%; Iyama and Idu, 2015). If the use of *N. latifolia* and *N. diderrichii* is heavily documented in the Southern Nigeria (Gbile and Adesina, 1987; Odugbemi et al., 2007; Ajibesin et al., 2008; Adebayo and Krettli, 2011; Dike et al., 2012; Olorunnisola et al., 2013; Iyama and Idu, 2015; Chukwuma, 2015), antimalarial ethnopharmacological data about the genus have been recorded in neighboring countries such as Cameroon (Betti, 2004; Ndenecho, 2009; Tsabang et al., 2012), Benin (Yetein et al., 2013), Togo (Koudouvo et al., 2011) or Ghana (Asase et al., 2005, Asase and Oppong-Mensah, 2009, Asase et al., 2010), and more generally over a wide geographical area from Senegal to the Democratic Republic of Congo (Table 2). Interestingly, if the active extracts are most often prepared as decoctions, various plant parts (leaves, roots, bark) are used, even within the same region.

Table 2. Anti-malarial uses of African *Nauclea* species

<i>Species</i>	<i>Plant part (extraction mode)</i>	<i>Country</i>	<i>Region</i>	<i>% of citation</i>	<i>Administration mode (Dose)</i>	<i>Reference</i>
<i>N. diderrichii</i>	B (d)	Benin	Plateau of Allada	52%		Yetein et al., 2013
<i>N. diderrichii</i>		Cameroon	Dja Biosphere Reserve			Betti, 2004
<i>N. diderrichii</i>	B, R, F	Cameroon	Mount Cameroon			Ndenecho, 2009
<i>N. diderrichii</i>		Ivory Coast	Tanoé-Ehy Forest			Zadou et al., 2011
<i>N. diderrichii</i>	R, SB, F	Nigeria				Chukwuma, 2015
<i>N. diderrichii</i>	SB (d)	Nigeria	South Nigeria	9%		Iyamah and Idu, 2015
<i>N. diderrichii</i>			Congo basin forests			Eto, 2013
<i>N. latifolia</i>	R, S	Burkina Faso				Kristensen and Balslev 2003
<i>N. latifolia</i>	R, L (d, m)	Burkina Faso	Baskoure, Kourittenga Province	12%		Nadembega et al., 2011
<i>N. latifolia</i>	SB, R (d)	Cameroon	Yaoundé & Mbalmayo			Tsabang et al., 2012
<i>N. latifolia</i>	R (d)	D.R. Congo	All regions	19%		Lusakibanza Manzo, 2012
<i>N. latifolia</i>	S (m)	Ghana	Accra, Central, Eastern & Ashanti Regions	9%		Asase and Oppong-Mensah, 2009
<i>N. latifolia</i>	R (m), L (d)	Ghana	Wechiau Community Hippopotamus Sanctuary area			Asase et al., 2005
<i>N. latifolia</i>	R (d)	Ghana	Dangme West District	21%		Asase et al., 2010
<i>N. latifolia</i>	RB (i)	Ghana	North West			Asase and Oteng-Yeboah, 2012
<i>N. latifolia</i>		Ghana				Osei-Djarbeng et al., 2015
<i>N. latifolia</i>	L, SB, RB (d)	Guinea	All regions	12%		Traore et al., 2013
<i>N. latifolia</i>	R	Guinea	Fuuta Jallon area			Kamsu-Foguem et al., 2013

<i>N. latifolia</i>	SB (d)	Mali			Ahua et al., 2007
<i>N. latifolia</i>	L (d), B (m)	Mali	All regions		Badiaga, 2011
<i>N. latifolia</i>	L (d, oral & bath)	Mali	Sélingué subdistrict	66%	Diarra et al., 2015
<i>N. latifolia</i>	L (d), B, R	Mali			Nordeng et al. 2013
<i>N. latifolia</i>	SB, R, L (m)	Nigeria	Middle Belt, Southern region		Adebayo and Krettli, 2011
<i>N. latifolia</i>	L	Nigeria	South-western	0.2%	Dike et al., 2012
<i>N. latifolia</i>	L (d)	Nigeria	Ogbomoso, South West		Olorunnisola et al., 2013
<i>N. latifolia</i>	R, (m, d, i)	Nigeria	Akwa Ibom State	3%	Ajibesin et al., 2008
<i>N. latifolia</i>	R, B, L (t, d)	Nigeria	Okeigbo, Ondo state, southwest		Odugbemi et al., 2007
<i>N. latifolia</i>	R, S, L	Nigeria	All regions		Gbile and Adesina, 1987
<i>N. latifolia</i>	L, SB, R (t, d)	Nigeria	Southern	46%,	Iyamah and Idu, 2015
<i>N. latifolia</i>	Combined plants	Nigeria			Abd El-Ghani, 2016
<i>N. latifolia</i>	L	Nigeria	Okigwe Imo State		Uzodimma, 2013
<i>N. latifolia</i>	L (i)	Nigeria	Ekiti state		Olorunniyi and Morenikeji, 2013
<i>N. latifolia</i>	B, R (d)	Nigeria	Ogun state		Adeyemi et al., 2010
<i>N. latifolia</i>	L	Nigeria	Ogun state		Adekunle, 2008
<i>N. latifolia</i>	B	Nigeria	SW		Omobuwajo et al., 2008
<i>N. latifolia</i>		Senegal			Kerharo and Adam, 1974
<i>N. latifolia</i>		Sierra Leone	Bo	50%	Ranasinghe et al., 2015
<i>N. latifolia</i>	L	Sierra Leone			Kanteh and Norman, 2015
<i>N. latifolia</i>	L (d), R (d)	Sierra-Leone	Kpaa Mende		Lebbie and Guries, 1995
<i>N. latifolia</i>	R (d, m)	Togo	Maritime region		Koudouvo et al., 2011
<i>N. latifolia</i>	AP (d)	Togo			Tittikpina et al., 2016
<i>N. latifolia</i>	R (m), L	Togo			Tchacondo et al., 2011

<i>N. latifolia</i>		Togo	Plateau region		Agbodeka et al., 2016
<i>N. pobeguinii</i>	SB (d)	D.R. Congo	District of Sankuru		Mesia et al., 2005
<i>N. pobeguunii</i>	SB (d, m)	D.R. Congo	All regions	17%	Lusakibanza Manzo, 2012
<i>N. pobeguunii</i>	SB (m)	Guinea	All regions	7%	Traore et al., 2013
<i>N. popeguinii</i>	L (d)	Mali	Sélingué subdistrict	55%	Diarra et al., 2015

Aerial parts (AP), Bark (B), Stem Bark (SB), Root (R), Root Bark (RB), Stem (S), Leaves (L), Fruit (F), decoction (d), maceration (m), infusion (i), tincture (t), Democratic Republic of Congo (D.R. Congo).

3.1.2. Anti-helminthic

From Sierra Leone to Angola, extracts of *N. latifolia* are used as anti-helminthic agents (Göhre et al., 2016) (Table 5). The roots, bark, stem or leaves are prepared, often through decoction, and consumed as vermifuge (Lebbie and Guries, 1995; Abd El-Ghani, 2016; Ahombo et al., 2012; Kanteh and Norman, 2015; Tittikpina et al., 2016) and for the management of helminthiasis of humans and animals (Agyare et al., 2014). The stem bark decoctions of *N. diderrichii* and *N. pobeguunii* have also been described as traditional anti-helminthic remedies in D.R. Congo (Mesia et al., 2005; Mbuta et al., 2012; Lusakibanza Manzo, 2012).

Table 5. Anti-helminthic uses of African *Nauclea* species

<i>Species</i>	<i>Plant part (extraction mode)</i>	<i>Country</i>	<i>Region</i>	<i>% of citation</i>	<i>Administration mode (Dose)</i>	<i>Reference</i>
<i>N. diderrichii</i>	SB (d)	D.R. Congo	Equateur Province	nd	Enema (half a glass twice daily), oral intake	Mbuta et al., 2012
<i>N. latifolia</i>	R, B (directly consumed, m, d)	Angola	Uige	Most cited plant ^a	Enema or oral intake	Göhre et al., 2016
<i>N. latifolia</i>	R (d)	Congo	Brazzaville	11% ^a	nd	Ahombo et al., 2012

<i>N. latifolia</i>		Ghana	Ashanti region	2%	nd		Agyare et al., 2014
<i>N. latifolia</i>	S, L	Nigeria	Nasarawa state	3%	nd		Ibrahim et al., 2016
<i>N. latifolia</i>	L (d)	Sierra Leone		nd	Application on the belly		Kanteh and Norman, 2015
<i>N. latifolia</i>	R, L (d)	Sierra-Leone	Kpaa Mende	nd	Oral intake (with <i>Cassia sieberiana</i>)		Lebbie and Guries, 1995
<i>N. latifolia</i>	AP (d)	Togo		nd	nd		Tittikpina et al., 2016
<i>N. pobeguinii</i>	SB (d)	D.R.Congo	District of Sankuru	nd	nd		Mesia et al., 2005
<i>N. pobeguunii</i>	SB (d, m)	D.R.Congo	All regions	nd	nd		Lusakibanza Manzo, 2012

Aerial parts (AP), Stem Bark (SB), Root (R), Stem (S), Leaves (L), decoction (d), maceration (m), Democratic Republic of Congo (D.R.Congo); ^a: including other indications.

3.1.3. Antiviral

Similarly, *N. latifolia* intakes have been heavily reported in Nigeria for treating viral diseases such as jaundice, yellow fever or measles (Gbile and Adesina, 1987) (Table 3). *N. latifolia* is also consumed in Sierra Leone for its effect against yellow fever, flu and measles (Lebbie and Guries, 1995). Interestingly, it was also cited among the most frequently used herbal medicine for the management of HIV/AIDS in Uganda (Lamorde et al., 2010). The use of *N. diderrichii*, although far less mentioned, has been reported in Gabon (Betti et al., 2013) and Democratic Republic of Congo (Mbuta et al., 2012) for treating jaundice and hepatitis respectively.

Table 3. Anti-viral uses of African *Nauclea* species

Traditional use	Species	Plant part (extraction mode)	Country	Region	% of citation	Administration mode (Dose)	Reference
Jaundice	<i>N. diderrichii</i>	W (d)	Gabon	Ipassa Biosphere Reserve	1%	Oral intake, enema	Betti et al., 2013
	<i>N. latifolia</i>	L, R (i)	Nigeria	All regions	nd	nd	Gbile and Adesina, 1987

	<i>N. latifolia</i>	R (d)	Nigeria	Ogun state	nd	Oral intake (1 cup daily)	Erinoso and Aworinde, 2012
	<i>N. latifolia</i>	R	Nigeria	Abeokuta	nd	Oral intake (1 small cup daily)	Idu et al., 2010
Yellow fever	<i>N. latifolia</i>	Inner B, S, sap, R, F, RB	Nigeria	Lagos state	nd	nd	Olowokudejo et al., 2008
	<i>N. latifolia</i>	R	Nigeria	Enugu state	nd	Oral intake (1 glass thrice daily)	Aiyeloja and Bello, 2006
	<i>N. latifolia</i>	(d)	Nigeria	Ogun state	11% ^a	Several recipes with other plants	Adeyemi et al., 2010
	<i>N. latifolia</i>	R (m)	Nigeria	Benue state	nd	nd	Shomkegh et al., 2016
	<i>N. latifolia</i>	L (d)	Sierra-Leone	Kpaa Mende	nd	Bath (in combination with other plants)	Lebbie and Guries, 1995
Hepatitis	<i>N. diderrichii</i>	B (d)	D.R. Congo	Equateur Province	nd	Oral intake (1 glass twice daily during 7 days)	Mbuta et al., 2012
AIDS	<i>N. latifolia</i>	R, RB	Uganda	Sembabule, Kamuli, Kabale and Gulu districts	20% ^b	nd	Lamorde et al., 2010
Measles	<i>N. latifolia</i>	Inner B, S, sap, R, F, RB	Nigeria	Lagos state	nd	nd	Olowokudejo et al., 2008
Flu and measles	<i>N. latifolia</i>	R	Sierra-Leone	Kpaa Mende	nd	nd	Lebbie and Guries, 1995

Bark (B), Root (R), Root Bark (RB), Stem (S), Leaves (L), Fruit (F), Wood (W), decoction (d), infusion (i), Democratic Republic of Congo (D.R.Congo); ^a: including other indications, ^b: specific study on this indication.

3.1.4. Antimicrobial

As a treatment for dysentery and diarrhea, *N. latifolia*, *N. diderrichii* and *N. pobeguini* have been reported in Ivory Coast (Zadou et al., 2011; Ambe, 2015), Nigeria (Chukwuma et al., 2015), Gabon (Betti et al., 2013), Uganda (Lamorde et al., 2010), Sierra Leone (Oliver-Bever, 1983; Kanteh and Norman, 2015), Congo (Ahombo et al., 2012), Gambia (Madge, 1998) and Ghana (Sam et al., 2013) (Table 4). The bark of *N. latifolia* is also used to cure or prevent sexually transmitted infections, especially in Nigeria (Uzodimma, 2013; Gbadamosi and

Egunyomi, 2014). Among the reported venereal diseases, gonorrhoea was more specifically targeted by *Nauclea*-based traditional remedies: the use of the roots and stem barks of *N. latifolia*, *N. diderrichii* and *N. pobeguinii* has been described in Nigeria (MacDonald and Olorunfemi, 2000; Ajibesin et al., 2012a; Chukwuma et al., 2015), but also in Congo (Ahombo et al., 2012) and D.R. Congo (Mesia et al., 2005; Lusakibanza Manzo, 2012). Besides these indications, extracts of *Nauclea* species are used by local populations for a variety of infectious diseases (Magassouba et al., 2007; Lawal et al., 2010; Badiaga, 2011; Sourabié et al., 2013), including scalp infections and abscess of children (Aworinde and Erinoso, 2015), gale (Lebbie and Guries, 1995; Zadou et al., 2011), thrush (Olowokudejo et al., 2008), lepra (Nadembega et al., 2011), typhoid (Ndenecho, 2009; Adeyemi et al., 2010; Göhre et al., 2016), tuberculosis (Mann et al., 2007) or ringworm (Ibrahim et al., 2016). However, to date no studies revealed a particularly high frequency of citation of the *Nauclea* genus for these ailments.

Table 4. Anti-microbial uses of African *Nauclea* species

<i>Traditional use</i>	<i>Species</i>	<i>Plant part (extraction mode)</i>	<i>Country</i>	<i>Region</i>	<i>% of citation</i>	<i>Administration mode (Dose)</i>	<i>Reference</i>
General antimicrobial use	<i>N. latifolia</i>	SB (m)	Guinea	All regions	0.2%	Oral intake	Magassouba et al., 2007
	<i>N. latifolia</i>	L (d), F (m), B (d), R (m)	Mali	All regions	nd	nd	Badiaga, 2011
	<i>N. latifolia</i>	R (m)	Uganda	Bulamogi	nd	Oral intake (m in beer made from <i>Musa × paradisiaca</i> L. var. <i>sapientum</i>)	Tabuti et al., 2003
	<i>N. latifolia</i>		Nigeria	SW	nd	nd	Lawal et al. 2010
	<i>N. latifolia</i>	R, L	Burkina faso	Malon village	nd	nd	Sourabié et al. 2013
	<i>N. pobeguunii</i>	SB (m)	Guinea	All regions	0.5%	Oral intake	Magassouba et al., 2007

Scalp infecion	<i>N. latifolia</i>	R (d)	Nigeria	Ibadan	nd	Oral intake or bath (in combination with other plants)	Aworinde and Erinoso, 2015
Abcsess	<i>N. latifolia</i>	R (d)	Nigeria	Ibadan	nd	Oral intake or bath (in combination with other plants)	Aworinde and Erinoso, 2015
Gale	<i>N. diderrichii</i>		Ivory Coast	Tanoé-Ehy Forest	nd	nd	Zadou et al., 2011
	<i>N. latifolia</i>	L	Sierra-Leone	Kpaa Mende	nd	nd	Lebbie and Guries, 1995
Thrush	<i>N. latifolia</i>	Inner B, S, sap, R, F, RB	Nigeria	Lagos state	nd	nd	Olowokudejo et al., 2008
Lepra	<i>N. latifolia</i>	R ,L	Burkina Faso	Baskoure, Kourittenga Province	3% ^a	nd	Nadembega et al., 2011
Sexually transmitted infections	<i>N. latifolia</i>	B	Nigeria	Ibadan	2%	nd	Gbadamosi and Egunyomi, 2014
	<i>N. latifolia</i>	R, SB (d)	Nigeria	Okigwe Imo state	nd	Boiled with potash	Uzodimma, 2013
Gonorrhoea	<i>N. diderrichii</i>	R, SB, F	Nigeria		nd	nd	Chukwuma et al., 2015
	<i>N. latifolia</i>	R (d)	Congo	Brazzaville	11%	nd	Ahombo et al., 2012
	<i>N. latifolia</i>	R (d)	Nigeria	Rivers state	FL = 65	Oral intake (1 glass thrice daily)	Ajibesin et al., 2012a
	<i>N. pobeguinii</i>	R	Nigeria	Adamawa State	nd	nd	Mac Donald and Olorunfemi, 2000
	<i>N. pobeguinii</i>	SB (d)	D.R. Congo	District of Sankuru	nd	nd	Mesia et al., 2005
	<i>N. pobeguinii</i>	SB (d, m)	D.R. Congo	All regions	nd	nd	Lusakibanza Manzo, 2012
Typhoid	<i>N. diderrichii</i>	B, R, F	Cameroon	Mount Cameroon	nd	nd	Ndenecho, 2009
	<i>N. latifolia</i>	B, R (d)	Nigeria	Ogun state	3%	nd	Adeyemi et al., 2010
	<i>N. latifolia</i>	R (d)	Angola	Uige	Most cited plant ^a	Oral intake	Göhre et al., 2016
Dysentery / Diarrhoea	<i>N. diderrichii</i>		Ivory Coast	Tanoé-Ehy Forest	nd	nd	Zadou et al., 2011
	<i>N. diderrichii</i>	R, SB, F	Nigeria		nd	nd	Chukwuma et al., 2015
	<i>N. diderrichii</i>	SB (m)	Gabon	Ipasa Biosphere Reserve	1%	nd	Betti et al., 2013

<i>N. diderrichii</i>	R (d)	Ghana	Brong Ahafo	nd	Oral intake	Sam et al., 2013
<i>N. latifolia</i>	L	Ivory coast	Abidjan	1%	nd	Ambe et al., 2015
<i>N. latifolia</i>	L	Sierra Leone		nd	bath	Kanteh and Norman, 2015
<i>N. latifolia</i>	R, RB	Uganda	Sembabule, Kamuli, Kabale and Gulu districts	5% ^a	nd	Lamorde et al., 2010
<i>N. latifolia</i>	R (d)	Congo	Brazzaville	5%	nd	Ahombo et al., 2012
<i>N. latifolia</i>	B	The Gambia		nd	nd	Madge, 1998
<i>N. latifolia</i>	F	Sierra-Leone	Kpaa Mende	nd	nd	Oliver-Bever, 1983
<i>N. pobeguinii</i>	B	Ivory coast	Abidjan	0.2%	nd	Ambe et al., 2015

Bark (B), Stem Bark (SB), Root (R), Root Bark (RB), Stem (S), Leaves (L), Fruit (F), decoction (d), maceration (m), Democratic Republic of Congo (D.R.Congo); ^a: including other indications; FL (%) = $N_p/N \times 100$ (N_p is the number of informants that claim a use of a plant species to treat a particular disease and, N is the number of informants that use the plant as a medicine to treat any given disease).

3.2. Digestive disorders

Among *Nauclea* species, only *N. latifolia* and *N. diderrichii* are used by African population to cure digestive ailments (Mathias et al., 2013; Jiofack et al., 2010; Ubom, 2010; Eto, 2013) (Table 6). Several therapeutic indications are described all along central Africa from Sierra Leone to Uganda. *N. diderrichii* and *N. latifolia* are both reported as agents for dental and oral care, the later being used as chewing stick (Ndenecho, 2009; Kayode and Omotoyinbo, 2008). Various parts of the plant (i.e. stem, bark, root and fruit for *N. diderrichii* and stem, bark, root, leaf, sap and fruit for *N. latifolia*) are prescribed by traditional healers for stomach problem management (Eyong, 2007; Ndenecho, 2009; Sainge et al., 2014; Olowokudejo et al., 2008; Insoll, 2011; Taïta, 2003; Tchacondo et al., 2011). Constipation could also be treated by both

species (Lebbie and Guries, 1995; Betti, 2002). Additionally, *N. latifolia* is reported as emetic (Olowokudejo et al., 2008) while *N. diderrichii* is mentioned as purgative (Nadembega et al., 2011). *N. latifolia* is finally used for two other digestive system indications, i.e. hernia (Nadembega et al., 2011; Tabuti et al., 2003) and haemorrhoids (Tchacondo et al. 2011; Taïta, 2003; Ngbolua et al., 2016).

Table 6. Uses of African *Nauclea* species as digestive disorders treatment

<i>Traditional use</i>	<i>Species</i>	<i>Plant part (extraction mode)</i>	<i>Country</i>	<i>Region</i>	<i>% of citation</i>	<i>Administration mode (Dose)</i>	<i>Reference</i>
Dental and oral care	<i>N. diderrichii</i>	B, R, F	Cameroon	Mount Cameroon	nd	nd	Ndenecho, 2009
	<i>N. latifolia</i>	S	Nigeria	Ekiti state	nd	Chewing stick	Kayode and Omotoyinbo, 2008
Digestive ailments	<i>N. latifolia</i>		Nigeria	Kaduna state	nd	nd	Mathias et al., 2013
Facilitate Digestion	<i>N. latifolia</i>	F (eating)	Cameroon	Sudano-sahelian	low	nd	Jiofack et al., 2010
	<i>N. diderrichii</i>	B (d)	Nigeria	Niger delta	nd	Enema	Ubom, 2010
	<i>N. diderrichii</i>			Congo basin forests	nd	nd	Eto, 2013
Emetic	<i>N. latifolia</i>	Inner B, S, sap, R, F, RB	Nigeria	Lagos state	nd	nd	Olowokudejo et al. 2008
Stomach problems	<i>N. diderrichii</i>	B, R, S		Central Africa	nd	nd	Eyong, 2007
	<i>N. diderrichii</i>	B, R, F	Cameroon	Mount Cameroon	nd	nd	Ndenecho, 2009
	<i>N. latifolia</i>	F, B, R	Cameroon	Mbembe Forest Reserve	nd	nd	Saingé et al., 2014
	<i>N. latifolia</i>	Inner B, S, sap, R, F, RB	Nigeria	Lagos state	nd	nd	Olowokudejo et al. 2008
	<i>N. latifolia</i>		Ghana	Northern	nd	Oral intake or bath	Insoll, 2011
	<i>N. latifolia</i>	L (i)	Burkina Faso	Western	nd	nd	Taïta, 2003

	<i>N. latifolia</i>	R (powder)	Togo	Tem tribe	32%	Oral intake	Tchacondo et al., 2011
Constipation	<i>N. diderrichii</i>			Congo basin forests	nd	nd	Eto, 2013
	<i>N. latifolia</i>	L, R (d)	Sierra-Leone	Kpaa Mende	nd	Oral intake	Lebbie and Guries, 1995
Purgative	<i>N. diderrichii</i>	SB	Cameroon	Yaoundé markets	0.8%	nd	Betti, 2002
Hernia	<i>N. latifolia</i>	R, L	Burkina Faso		3% ^a	nd	Nadembega et al., 2011
	<i>N. latifolia</i>	R, F (m)	Uganda	Bulamogi	nd	nd	Tabuti et al., 2003
Haemorrhoids	<i>N. latifolia</i>	L (d)	Togo	Tem tribe	26% ^a	Oral intake or emena	Tchacondo et al., 2011
	<i>N. latifolia</i>	R, B (d)	Burkina Faso	Western	nd	nd	Taïta, 2003
	<i>N. latifolia</i>	R	Congo	Kinshasa city	6%	Oral intake (2 glasses daily)	Ngbolua et al., 2011

Bark (B), Stem Bark (SB), Root (R), Root Bark (RB), Stem (S), Leaves (L), Fruit (F), decoction (d), maceration (m); ^a: including other indications.

3.3. Pain management

Pain management by *Nauclea* genus extract has been widely described. The most frequent indication is abdominal- or stomach-ache for which root, leaf, bark and fruit of *N. latifolia* are used in several countries along an arc from Senegal to Angola (Adamu et al., 2005; Lekana-Douki et al., 2011; Nadembega et al., 2011; Badiaga, 2011; Lusakibanza Manzo, 2012; Gning et al., 2014; Göhre et al., 2016; Madge, 1998; Kristensen and Balslev, 2003) (Table 7). *N. pobeguinii* stem bark decoction is mentioned for the same symptoms in D.R. Congo (Mesia et al., 2005). Root, leaf, and fruit of *N. latifolia* are consumed to treat backache in Nigeria, D.R. Congo and Uganda (Tabuti et al., 2003; Ngbolua et al., 2016; Amusa et al., 2010) while *N. diderrichii* stem bark is indicated for lumbago in Cameroon (Betti, 2002). Two additional traditional uses of bark, root or fruit of this plant are described, i.e. toothache and headache (Ndenencho, 2009). *N. latifolia* leaves are also used for the later indication (Badiaga, 2011; Lekana-Douki et al., 2011).

Table 7. Uses of African *Nauclea* species as analgesic

<i>Traditional use</i>	<i>Species</i>	<i>Plant part (extraction mode)</i>	<i>Country</i>	<i>Region</i>	<i>% of citation</i>	<i>Administration mode (Dose)</i>	<i>Reference</i>
Toothache	<i>N. diderrichii</i>	B, R, F	Cameroon	Mount Cameroon	nd	nd	Ndenecho, 2009
Headache	<i>N. diderrichii</i>	B, R, F	Cameroon	Mount Cameroon	nd	nd	Ndenecho, 2009
	<i>N. latifolia</i>	L (d)	Mali	All regions	nd	Bath or oral intake (1 glass thrice or 4 times daily)	Badiaga, 2011
	<i>N. latifolia</i>		Gabon	Haut-Ogooué Province	nd	nd	Lekana-Douki et al., 2011
Abdominal- / stomach-ache	<i>N. latifolia</i>	B	Nigeria	Bauchi State	nd	nd	Adamu et al., 2005
	<i>N. latifolia</i>		Gabon	Haut-Ogooué Province	nd	nd	Lekana-Douki et al., 2011
	<i>N. latifolia</i>	R, L	Burkina Faso	Baskoure, Kourittenga Province	3% ^a	nd	Nadembega et al., 2011
	<i>N. latifolia</i>	B (d, m), R (d, m)	Mali	All regions	nd	Oral intake (1 glass twice or thrice daily) or emena	Badiaga, 2011
	<i>N. latifolia</i>	R (d)	D.R. Congo	All regions	19% ^a	nd	Lusakibanza Manzo, 2012
	<i>N. latifolia</i>	L, R (i)	Senegal	Kédougou	2% ^a	nd	Gning et al., 2014
	<i>N. latifolia</i>	R (m, d)	Angola	Uige	Most cited plant ^a	Oral intake or emena	Göhre et al., 2016
	<i>N. latifolia</i>	R	Gambia		nd	nd	Madge, 1998
	<i>N. latifolia</i>	R, F, L	Burkina Faso		0.7%	nd	Kristensen and Balslev, 2003
	<i>N. pobeguinii</i>	SB (d)	D.R. Congo	District of Sankuru	nd	nd	Mesia et al., 2005
Backache	<i>N. latifolia</i>	R, F (i)	Uganda	Bulamogi	nd	nd	Tabuti et al., 2003
	<i>N. latifolia</i>	R	D.R. Congo	Kinshasa city	medium	nd	Ngbolua et al., 2016

	<i>N. latifolia</i>	R (d), L (d)	Nigeria	Kainji Lake National Park	nd	Oral intake or bath	Amusa et al., 2010
Lumbago	<i>N. diderrichii</i>	SB	Cameroon	Yaoundé markets	1%	nd	Betti, 2002

Bark (B), Stem Bark (SB), Root (R), Leaves (L), Fruit (F), decoction (d), maceration (m), infusion (i), Democratic Republic of Congo (D.R. Congo); ^a: including other indications.

3.4. Fever

Many authors reported the use of *N. diderrichii* or *N. latifolia* to manage fever (Table 8). Sometimes this indication is overlapped with antimalarial without any mention of whether these plants act as an etiologic treatment or as antipyretic. For example, in central Africa *N. diderrichii* is indicated to treat fever (Eyong, 2007; Eto, 2013) and especially during malaria (Betti, 2004). Same uses of all parts of *N. latifolia* are described in different states of Nigeria (Olowokudejo et al., 2008; Igoli et al., 2005) especially among Tiv people who placed it as leader plant against fever in their traditional medical system (Igoli et al., 2011). The roots and bark of the same species are also exploited in Gambia (Madge, 1998).

Table 8. Uses of African *Nauclea* species as antipyretic

<i>Species</i>	<i>Plant part (extraction mode)</i>	<i>Country</i>	<i>Region</i>	<i>% of citation</i>	<i>Administration mode (Dose)</i>	<i>Reference</i>
<i>N. diderrichii</i>		Cameroon	Dja Biosphere Reserve	nd	nd	Betti, 2004
<i>N. diderrichii</i>	B, R, S		Central Africa	nd	nd	Eyong, 2007
<i>N. diderrichii</i>			Congo basin forests	nd	nd	Eto, 2013
<i>N. latifolia</i>	Inner B, S, sap, R, F, RB	Nigeria	Lagos state	nd	nd	Olowokudejo et al., 2008
<i>N. latifolia</i>	L (d)	Nigeria	Tivland	2%	nd	Igoli et al., 2011
<i>N. latifolia</i>	L	Nigeria	Igede People	nd	nd	Igoli et al., 2005
<i>N. latifolia</i>	R, B	Gambia		nd	nd	Madge, 1998

Bark (B), Root (R), Root Bark (RB), Stem (S), Leaves (L), Fruit (F), decoction (d).

3.5. Respiratory diseases

Fumigations of *N. latifolia* seeds are prescribed in D.R. Congo against respiratory diseases (Disengomoka et al., 1983) (Table 9), and the bark of this plant is directly consumed for the same indication in Angola (Göhre et al., 2016). A recipe using *N. latifolia* in combination with several other plants is used against asthma in Nigeria (Fatokun et al., 2016). Cough management using bark, root or fruit of *N. diderrichii* (Ndenecho, 2009) or various part of *N. latifolia* (Olowokudejo et al., 2008; Lebbie and Guries, 1995), is also reported.

Table 9. Uses of African *Nauclea* species as respiratory diseases treatment

<i>Traditional use</i>	<i>Species</i>	<i>Plant part (extraction mode)</i>	<i>Country</i>	<i>Region</i>	<i>% of citation</i>	<i>Administration mode (Dose)</i>	<i>Reference</i>
General use	<i>N. latifolia</i>	Seeds	D.R. Congo	All regions	nd	Fumigation (twice daily)	Disengomoka et al., 1983
	<i>N. latifolia</i>	B	Angola	Uige	Most cited plant ^a	Directly consumed	Göhre et al., 2016
Cough	<i>N. diderrichii</i>	B, R, F	Cameroon	Mount Cameroon	nd	nd	Ndenecho, 2009
	<i>N. latifolia</i>	Inner B, S, sap, R, F, RB	Nigeria	Lagos state	nd	nd	Olowokudejo et al., 2008
	<i>N. latifolia</i>	Inner B	Sierra-Leone	Kpaa Mende	nd	nd	Lebbie and Guries, 1995
Asthma	<i>N. latifolia</i>	multiplant combination (m)	Nigeria	Western	nd	Oral intake (1 glass daily)	Fatokun et al., 2016

Bark (B), Root (R), Root Bark (RB), Stem (S), Fruit (F), Democratic Republic of Congo (D.R.

Congo); ^a: including other indications.

3.6. Metabolic and cardio-vascular disorders

Many mentions of treatments against metabolic diseases using *Nauclea* are reported in West African countries (Table 10). Diabetes management is mentioned for three species: *N. pobeguinii* (leaf and bark) (Baldé et al., 2006), *N. latifolia* (root, stem bark, leaf and fruit) (Fah et al., 2013; Muziazia et al., 2015; Ngbolua et al. 2016; N’Guessan et al. 2009; Gigado et al., 2005; Baldé et al., 2006) and *N. diderrichii* (bark) (Laleye et al., 2015; Nole et al., 2016). The two later species are also indicated as diuretics using root, bark or fruit (Ahombo et al., 2012; Nadembega et al., 2011; Nole et al., 2016; Ndenecho, 2009). Various parts (i.e. leaf, root and stem) of *N. latifolia* are used as antihypertensive agents (Gbolade, 2012; Lagnika et al., 2016) especially roots that have been highly cited for this indication in the Southwestern Nigeria (Olorunnisola et al., 2015). Fruits are also mentioned as appetite suppressant (Pare et al., 2016). *N. diderrichii* bark, root and fruit are reported as blood thinner (Ndenecho, 2009) and bark decoction is depicted as anti-anaemia (Yetein et al., 2013).

Table 10. Uses of African *Nauclea* species as metabolic and cardio-vascular disorders treatment

<i>Traditional use</i>	<i>Species</i>	<i>Plant part (extraction mode)</i>	<i>Country</i>	<i>Region</i>	<i>% of citation</i>	<i>Administration mode (Dose)</i>	<i>Reference</i>
Anti-diabetic	<i>N. diderrichii</i>		Benin		1%	nd	Laleye et al., 2015
	<i>N. diderrichii</i>	B (d)	Cameroon	Coastal rain forest	nd	Oral intake (2 glasses thrice daily)	Nole et al., 2016
	<i>N. latifolia</i>	R	Benin	Cotonou, Abomey-Calavi	0.5%	nd	Fah et al., 2013
	<i>N. latifolia</i>	R (d)	Congo		nd	nd	Muziazia et al., 2015
	<i>N. latifolia</i>	R	Congo	Kinshasa city	medium	Oral intake (2 glasses daily)	Ngbolua et al., 2016
	<i>N. latifolia</i>	SB (d)	Ivory Cost	Agbovill e	nd	Oral intake	N’Guessan et al., 2009

	<i>N. latifolia</i>	SB (d)	Guinea	Coastal lowlands	nd	nd	Gidado et al., 2005
	<i>N. latifolia</i>	L, F, R, B	Guinea	Conakry	3% ^a	nd	Baldé et al., 2006
	<i>N. pobequinii</i>	L, B	Guinea	Conakry	8% ^a	nd	Baldé et al., 2006
Diuretic	<i>N. latifolia</i>	R, L	Burkina Faso	Baskoure	0.7% ^b	nd	Nadembega et al., 2011
	<i>N. latifolia</i>	R (d)	Congo	Brazzaville	13% ^b	nd	Ahombo et al., 2012
	<i>N. diderrichii</i>	B (d)	Cameroon	Coastal rain forest	nd	Oral intake (2 glasses thrice daily)	Nole et al., 2016
	<i>N. diderrichii</i>	B, R, F	Cameroon	Mount Cameroon	nd	nd	Ndenecho, 2009
Anti-hypertensive	<i>N. latifolia</i>	L, R, S	Nigeria	Edo State	2%	Oral intake (1/2 or 1 glass daily)	Gbolade, 2012
	<i>N. latifolia</i>	R	Nigeria	Ogbomoso	30% ^c	Oral intake (1 tablespoon daily)	Olorunnisola et al., 2015
	<i>N. latifolia</i>	R (d)	Benin	Ouémé	3%	Oral intake	Lagnika et al., 2016
Blood thinner	<i>N. diderrichii</i>	B, R, F	Cameroon	Mount Cameroon	nd	nd	Ndenecho, 2009
Anaemia	<i>N. diderrichii</i>	B (d)	Benin	Plateau of Allada	34% ^b	nd	Yetein et al., 2013
Appetite suppressant	<i>N. latifolia</i>	F	Burkina faso		3%	Raw fruits consumption	Pare et al., 2016

Bark (B), Stem Bark (SB), Root (R), Stem (S), Leaves (L), Fruit (F), decoction (d); ^a: percentage of users; ^b: including other indications; ^c: specific study on cardiovascular diseases.

3.7. Reproduction and sexual dysfunctions

The three most ethnopharmacologically relevant species *N. latifolia*, *N. diderrichii* and *N. pobequinii* are indicated for treating sexual and reproductive dysfunctions (Table 11). Stem bark of *N. pobequinii* in D.R. Congo (Mesia et al., 2005; Lusakibanza Manzo, 2012) and bark of *N. diderrichii* in Cameroon and Gabon (Nole et al., 2016; Towns, 2014a) are reported for managing sexual asthenia. Infusion of *N. latifolia* root is used in case of premature ejaculation

(Tabuti et al., 2003) and more generally root or root bark are prescribed for male sexual dysfunction (Fasola et al., 2014; Göhre et al., 2016; Badiaga, 2011). *N. diderrichii* leaves are also consumed for the same indication (Betti et al., 2013). Female infertility is also treated by *N. latifolia* leaf, root or bark preparations (Nadembega et al., 2011; Nkounkou-Loumpangou et al., 2005; Makinde et al., 2015; Tchacondo et al., 2011) and by *N. diderrichii* stem bark extracts (Betti, 2002). Other authors also mentioned indication of *N. latifolia* bark for reproductive health (Diame, 2010) and of root for woman health (Quiroz, 2015) without further precision. Almost every parts of *N. latifolia* (except leaves) are reported for addressing menstrual disorders (Olowokudejo et al., 2008; Omobuwajo et al., 2008; Towns and Van Andel, 2014b). Anti-abortifacient effects are described for *N. pobeguinii* bark while *N. latifolia* root are reported abortifacient (Vaughan, 1997) and useful against uterine fibroids (Tabuti et al., 2003).

Table 11. Uses of African *Nauclea* species as reproduction and sexual dysfunctions treatment

<i>Traditional use</i>	<i>Species</i>	<i>Plant part (extraction mode)</i>	<i>Country</i>	<i>Region</i>	<i>% of citation</i>	<i>Administration mode (Dose)</i>	<i>Reference</i>
Sexual asthenia	<i>N. diderrichii</i>	B (d)	Cameroon	Coastal rain forest	nd	Oral intake (2 glasses thrice daily)	Nole et al., 2016
	<i>N. diderrichii</i>	B, W	Gabon	Mont Bouët and Ngouema	nd	nd	Towns, 2014a
	<i>N. pobeguunii</i>	SB (d, m)	D.R. Congo		nd	nd	Mesia et al., 2005
	<i>N. pobeguunii</i>	SB (d, m)	D.R. Congo	All regions	nd	nd	Lusakibanza Manzo, 2012
Premature ejaculation	<i>N. latifolia</i>	R (i)	Uganda	Bulamogi	nd	nd	Tabuti et al., 2003
Male sexual dysfunction	<i>N. diderrichii</i>	L (t)	Gabon	Ipassa Biosphere Reserve	nd	Oral intake	Betti et al., 2013
	<i>N. latifolia</i>	RB (alcohol)	Ethiopia and Nigeria	Ethiopia West and Delta state of Nigeria	nd	Oral intake (4-5 tablespoon twice daily)	Fasola et al. 2014
	<i>N. latifolia</i>	R (directly consumed or d)	Angola	Uige	Most cited plant ^a	Oral or enema	Göhre et al., 2016

	<i>N. latifolia</i>	R (d)	Mali	Bandiagara	nd	Oral intake (3 glasses thrice daily)	Badiaga, 2011
Female infertility	<i>N. diderrichii</i>	SB	Cameroon	Yaoundé markets	0.6%	nd	Betti, 2002
	<i>N. latifolia</i>	R, L	Burkina Faso		0.7% ^a	nd	Nadembega et al., 2011
	<i>N. latifolia</i>	L, R (d)	Congo	Brazzaville	12% ^b	Oral intake in combination with other plants (1/2 glass daily)	Nkounkou-Loumpangou et al., 2005
	<i>N. latifolia</i>	R, B (tincture), R (i in alcohol)	Nigeria	Lagos state	nd	nd	Makinde et al., 2015
	<i>N. latifolia</i>	R (d)	Togo		Most cited plant ^a	nd	Tchacondo et al., 2011
Menstrual disorder	<i>N. latifolia</i>	Inner B, S, sap, R, F, RB	Nigeria	Lagos state	nd	nd	Olowokudejo et al., 2008
	<i>N. latifolia</i>	B	Nigeria	Southwestern	nd	nd	Omobuwajo et al., 2008
	<i>N. latifolia</i>	R	Benin and Gabon	d	Most cited plant ^b	nd	Towns and Van Andel, 2014b
Reproductive health	<i>N. latifolia</i>	B	Ghana	Western	0.1%	nd	Diame, 2010
Women's health	<i>N. latifolia</i>	R (dry)	Benin		nd	bath	Quiroz, 2015
Uterine fibroids	<i>N. latifolia</i>	R	Uganda	Bulamogi	nd	nd	Tabuti et al., 2003
Anti-abortifacient	<i>N. pobeguinii</i>	B	Cameroon	Upper Nyong valley forest	nd	nd	Jiofack et al., 2009,
	<i>N. pobeguunii</i>	B	Cameroon	All regions	nd	nd	Njamen et al., 2013
Effective abortifacient	<i>N. latifolia</i>	R	Ghana		nd	nd	Vaughan, 1997

Bark (B), Stem Bark (SB), Root (R), Root Bark (RB), Stem (S), Leaves (L), Fruit (F), decoction (d), maceration (m), infusion (i), Democratic Republic of Congo (D.R.Congo); ^a: including other indications; ^b: specific study on this indication.

3.8. Skin disorders

Dermatologic indications of the *Nauclea* genus are reported in five countries of West and central Africa (i.e. Senegal, Gambia, Sierra-Leone, Cameroon and Nigeria) (Table 12). *N. diderrichii* (bark, root, fruit and leaf) (Ndenecho, 2009; Mustapha et al., 2013) and *N. latifolia* (stem and root) (Kayode et al., 2015; Ajibesin, 2012b; Shomkegh et al., 2016) are used in skin diseases management. Itching could be treated by leaf or root extracts of *N. latifolia* (Shomkegh et al., 2016; Aniaya et al., 2016). This latter extract is also indicated for dermatosis (Erinoso et al., 2016) whereas leaves and bark of *N. vanderghuchtii* (Jiofack et al., 2010) are employed for wound healing. All parts of *N. latifolia* are also reported as capable of accelerating cicatrisation (Olowokudejo et al., 2008; Lebbie and Guries, 1995; Madge, 1998) while leaf infusion is described to stimulate burn recovery (Gning et al., 2014).

Table 12. Uses of African *Nauclea* species as skin disorders treatment

<i>Traditional use</i>	<i>Species</i>	<i>Plant part (extraction mode)</i>	<i>Country</i>	<i>Region</i>	<i>% of citation</i>	<i>Administration mode (Dose)</i>	<i>Reference</i>
Skin disease	<i>N. diderrichii</i>	B, R, F	Cameroon	Mount Cameroon	nd	nd	Ndenecho, 2009
	<i>N. diderrichii</i>	L	Nigeria	Keffi	29% ^a	nd	Mustapha et al., 2013
	<i>N. latifolia</i>	S	Nigeria	Ekiti state	FL = 88	nd	Kayode et al., 2015
	<i>N. latifolia</i>	R (d)	Nigeria	Rivers state	FL = 65	Oral intake (1 glass thrice daily for 5 days)	Ajibesin, 2012b
Itching	<i>N. latifolia</i>	R (d)	Nigeria	Benue state	nd	Bath (twice daily for 2 days)	Shomkegh et al., 2016
Itching & filariasis	<i>N. latifolia</i>	L, R	Nigeria	Kogi state	nd	nd	Aniaya et al., 2016
Infantile dermatosis	<i>N. latifolia</i>	R (d)	Nigeria	Odeda	3% ^a	Oral intake in combination with other plants (2-3 teaspoon thrice daily)	Erinoso et al. 2016

Dermatosis / wound	<i>N. vanderguchtii</i>	L, B	Cameroon	Sudano-sahelian	medium	nd	Jiofack et al., 2010
Wound	<i>N. latifolia</i>	Inner B, S, sap, R, F, RB	Nigeria	Lagos state	nd	nd	Olowokudejo et al., 2008
	<i>N. latifolia</i>	R, S	Sierra-Leone	Kpaa Mende	nd	nd	Lebbie and Guries, 1995
	<i>N. latifolia</i>	R	Gambia		nd	nd	Madge, 1998
Burn	<i>N. latifolia</i>	L (i)	Senegal	Kédougou	FL = 50	Bath	Gning et al., 2014

Bark (B), Root (R), Root Bark (RB), Stem (S), Leaves (L), Fruit (F), decoction (d), infusion (i); ^a: specific study on dermatologic indication; FL (%) = $N_p/N \times 100$ (N_p is the number of informants that claim a use of a plant species to treat a particular disease and, N is the number of informants that use the plant as a medicine to treat any given disease).

3.9. Miscellaneous

N. latifolia is also used for ophthalmologic indications. In Sierra-Leone sap oozing from stem is instilled in eyes to improve sight or to cure eye troubles (Kanteh and Norman, 2015; Lebbie and Guries, 1995). Leaf decoction is as well used in Ivory Coast for conjunctivitis healing as ocular bath solution (Adiko et al., 2014) (Table 13).

Aqueous extract of *N. latifolia* leaf is indicated in Ethiopia for swollen spots on the head of children (Mengesha, 2016). Two parts of this plant (i.e. fruit and root) are also used for thin children to restore their appetite (Madge, 1998; Kristensen and Balslev, 2003).

Other sporadic therapeutic indications of the genus *Nauclea* are mentioned such as cataplasm for fractured bones (Thomas, 1959) (Table 13). *N. latifolia* is also used for rheumatism (Madge, 1998), for traumatic injuries of central nervous system (Kantati et al., 2016), as anticancer agent (Ashidi et al., 2010) or more generally for good health (Kristensen and Balslev, 2003). Finally,

N. xanthoxylon root, leaf and bark are reported as a therapeutic plant parts in Angovè forest (Benin) without mention of indications (Dossou et al., 2012).

Furthermore, *N. latifolia* is reported for veterinary indications which totally overlap human indications (Table 13). Cardinale *et al.* described the utilization of root or bark to cure horses fever or hernia in Cameroon (Cardinale and Seignobos, 2004). Root, leaf or stem bark are mentioned as anti-helminthic (Abu et al., 2009; Swaleh, 1999) and anti-diarrheic (Souare et al., 2013; Offiah et al., 2011).

Table 13. Miscellaneous ethnopharmacological uses of African *Nauclea* species

<i>Traditional use</i>	<i>Species</i>	<i>Plant part (extraction mode)</i>	<i>Country</i>	<i>Region</i>	<i>% of citation</i>	<i>Administration mode (Dose)</i>	<i>Reference</i>
Ophthalmic							
Improve sight	<i>N. latifolia</i>	Sap	Sierra-Leone		nd	Ocular (drop sap in the affected eye)	Kanteh and Norman, 2015
Eye troubles	<i>N. latifolia</i>	Sap	Sierra-Leone	Kpaa Mende	nd	nd	Lebbie and Guries, 1995
Conjunctivitis	<i>N. latifolia</i>	L (d)	Ivory Coast	Abidjan	3% ^a	Ocular	Adiko et al., 2014
Infant illness							
Swollen spots on the head	<i>N. latifolia</i>	L (m)	Ethiopia	Mandura Woreda	nd	Oral intake (1 glass)	Mengesha, 2016
Thin children	<i>N. latifolia</i>	F	Gambia		nd	nd	Madge, 1998
	<i>N. latifolia</i>	R	Burkina Faso		0.1%	nd	Kristensen and Balslev, 2003
Others indications							
For good health	<i>N. latifolia</i>	R, L	Burkina Faso		0.1%	nd	Kristensen and Balslev, 2003
Rheumatism	<i>N. latifolia</i>	R	Gambia		nd	nd	Madge, 1998
Fractured bones	<i>Nauclea sp.</i>	L	C.A.R.		nd	nd	Thomas, 1959
SNC injuries	<i>N. latifolia</i>	L (d, bath)	Togo	All regions	19% ^b	nd	Kantati et al., 2016

Anticancer	<i>N. latifolia</i>	R, L (d)	Nigeria	South-western	nd	Oral intake	Ashidi et al., 2010
General use	<i>N. xanthoxylon</i>	B, L, R	Benin	Agonvè forest	medium	nd	Dossou et al., 2012
Veterinary uses							
Diarrhea	<i>N. latifolia</i>	R	Cameroon		nd	nd	Souare et al., 2013
	<i>N. latifolia</i>	L, SB, R	Nigeria	Plateau state	2% ^a	nd	Offiah et al., 2011
Anti-helminthic	<i>N. latifolia</i>	L, SB (m)	Nigeria	Nasarawa state	nd	nd	Abu et al., 2009
	<i>N. latifolia</i>	R (d)	Kenya	Ormaland	nd	nd	Swaleh, 1999
Horse fever	<i>N. latifolia</i>	R, B (d)	Cameroun	Gobo	nd	nd	Cardinale and Seignobos, 2004
Horse hernia		R					

Bark (B), Stem Bark (SB), Root (R), Leaves (L), Fruit (F), decoction (d), maceration (m), Central African Republic (C.A.R.); ^a: specific study on this indication; ^b: including other indications.

4. Phytochemistry

4.1. Steroids & saponins

The chemical composition of African *Nauclea* species have started to be unraveled in 1953, with the discovery of the steroid β -sitosterol and its palmitate ester as the first identified metabolites from *N. diderrichii* (King and Jurd, 1953). Several other triterpene derivatives were discovered during the following decades (Figure 4). A mixture of β -sitosterol fatty esters was reported in *N. diderrichii* (Adeoye et al., 1981) and β -sitosterol with two related glucosides were isolated from the roots of *N. latifolia* (Abreu et al., 2001a; Ngnokam et al., 2003). Nevertheless, quinovic acid derivatives are the most studied family of triterpene compounds in the genus. Indeed, quinovic acid itself, along with eleven glycosides (*e.g.* glucosyl, fucosyl, rhamnosyl and derivatives) and the 3-oxo analogue, were extracted from the bark of *N. diderrichii* (Adeoye and Waigh, 1983a; Lamidi et al., 1995a, 1995b, 1995c, 1997; Di Giorgio et al., 2006). These saponins are not specific to one species, as some compounds have also been

described in *N. pobeguinii* (Zeches et al., 1985; Mesia et al., 2010) and *N. latifolia* (Ngnokam et al., 2003; Ata et al., 2009). Two additional triterpenes were identified as rotundic acid and 3-acetoxy-11-oxo-urs-12-ene, respectively in the roots of *N. latifolia* (Ngnokam et al., 2003) and in the bark of *N. pobeguinii* (Kueté et al., 2015). The general steroid precursor squalene has also been found in *N. latifolia* (Ngnokam et al., 2003).

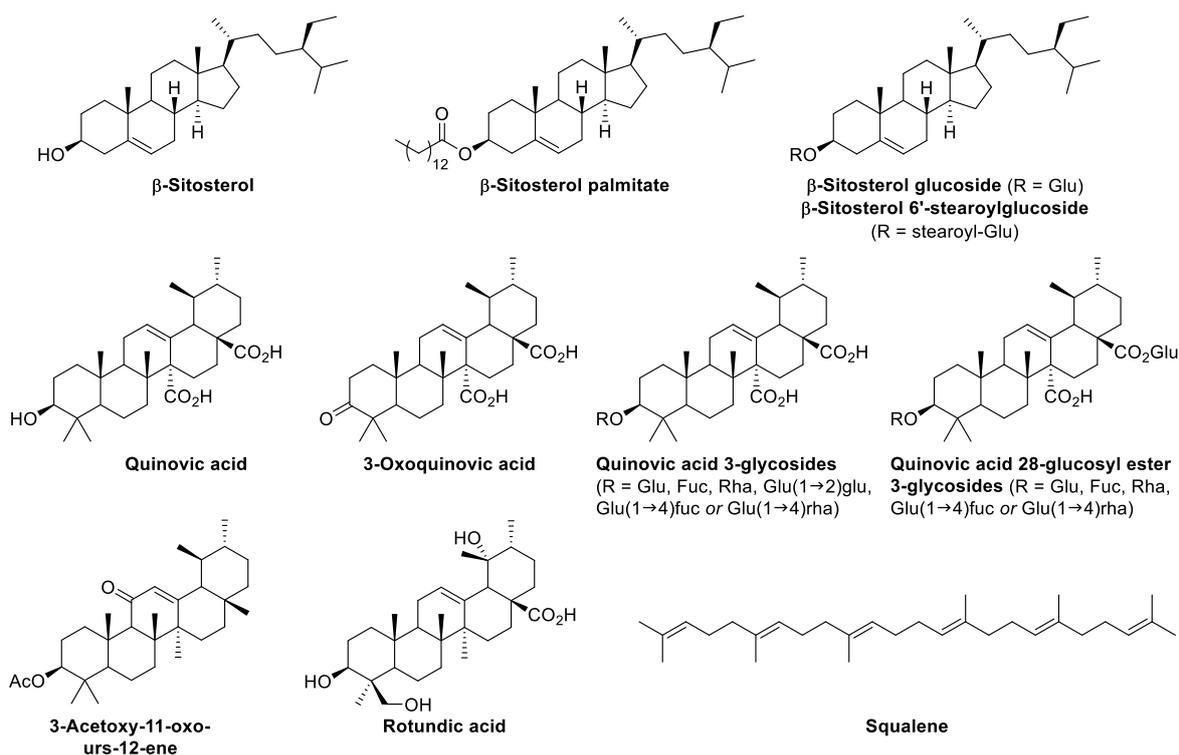


Figure 4. Structure of steroids and saponins isolated from African *Nauclea* species.

4.2. Alkaloids

A turning point was reached in phytochemical investigations of the *Nauclea* genus in 1970, with the description of several nicotinate derivatives, terpenoids and β -carbolines in the bark of *N. diderrichii* (Figures 5 and 6; MacLean and Murray, 1970, 1972a, 1972b). Interestingly, numerous alkaloid derivatives were isolated later as obvious biosynthetic adducts of these three classes of compounds, especially in *N. latifolia*, *N. diderrichii* and *N. pobeguunii*. Naucedine, desoxycordifolinic acid (*N. diderrichii*; MacLean and Murray, 1970; Murray et al., 1972; Adeoye and Waigh, 1983b), strictosidine, desoxycordifoline (*N. pobeguunii*; Xu et al., 2012)

and 3 α ,5 α -tetrahydrodesoxycordifoline (*N. pobeguinii*, *N. latifolia* and *N. diderrichii*; Lamidi et al., 1995c; Shigemori et al., 2003; Mesia et al., 2010) are five examples of β -carbolines modified through biosynthetic sequences involving either nicotinate (for naucleidine) or diderroside (for the four other compounds) derivatives (Figure 6).

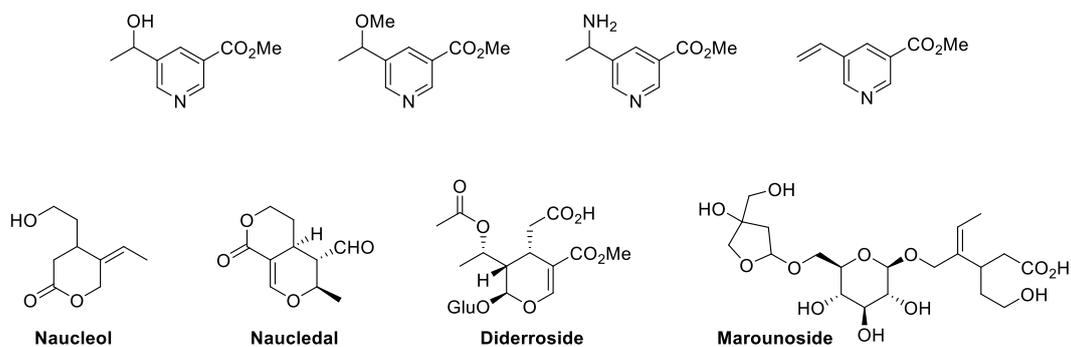


Figure 5. Structure of nicotinate and terpenoid derivatives isolated from African *Nauclea* species.

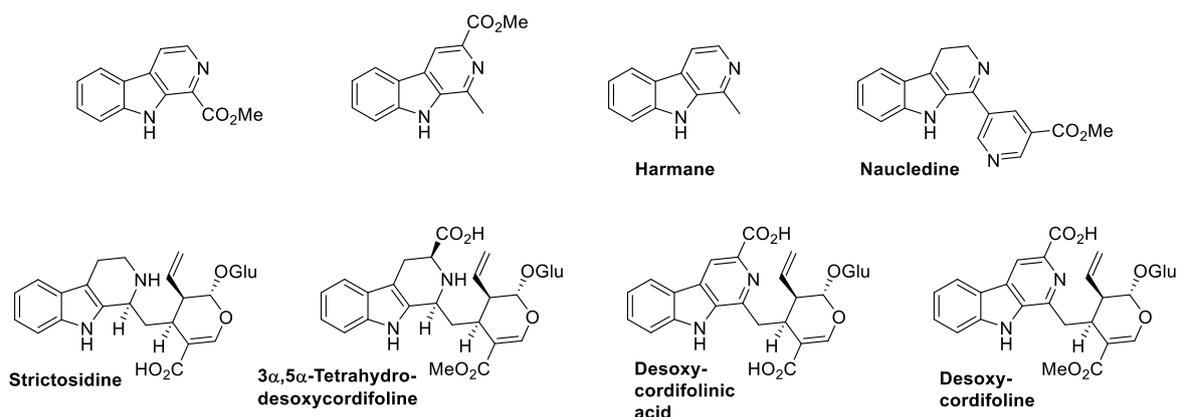


Figure 6. Structure of simple β -carbolines isolated from African *Nauclea* species.

A number of reported compounds from the class of indolo[2,3-*a*]quinolizidines are five-rings analogues of the aforementioned β -carbolines. Among them, a large series based on nauclefine contains no less than fourteen different structures (Figure 7). Besides the naked nauclefine, the 20-vinyl analogue angustine was extracted from the roots, stem bark and leaves of *N. latifolia*, and from the root bark of *N. pobeguunii* (Hotellier et al., 1975, 1979; Zeches et al., 1985; Abreu and Pereira, 1998, 2001b; Boumendjel et al., 2013). Several derivatives of angustine have also been discovered from *Nauclea* species: nauclefine (*N. latifolia*; Hotellier et al., 1975),

angustoline (*N. latifolia* and *N. pobeguinii*; Hotellier et al., 1975; Zeches et al., 1985; Abreu and Pereira, 1998, 2001b; Agomuoh et al., 2013), 19-*O*-methylangustoline (*N. pobeguinii*; Mesia et al., 2010), 19-*O*-ethylangustoline (*N. latifolia*; Abreu and Pereira, 1998, 2001b) and 19-*O*-acetylangustoline (*N. pobeguunii*; Zeches et al., 1985). Angustidine (Phillipson et al., 1982; Abreu and Pereira, 1998, 2001b) and naulafine (Hotellier et al., 1979) are particular derivatives from *N. latifolia*, respectively bearing a 21-methyl group and an additional fused ring. Furthermore, the 3,14-dihydro analogue of angustine has been described in the root bark of *N. pobeguunii* (Zeches et al., 1985), and several derivatives are also *Nauclea* constituents: 3,14-dihydroangustoline, 19-*O*-methyl-3,14-dihydroangustoline (*N. pobeguunii*; Xu et al., 2012), and latifoliamides D and E (*N. latifolia*; Agomuoh et al., 2013).

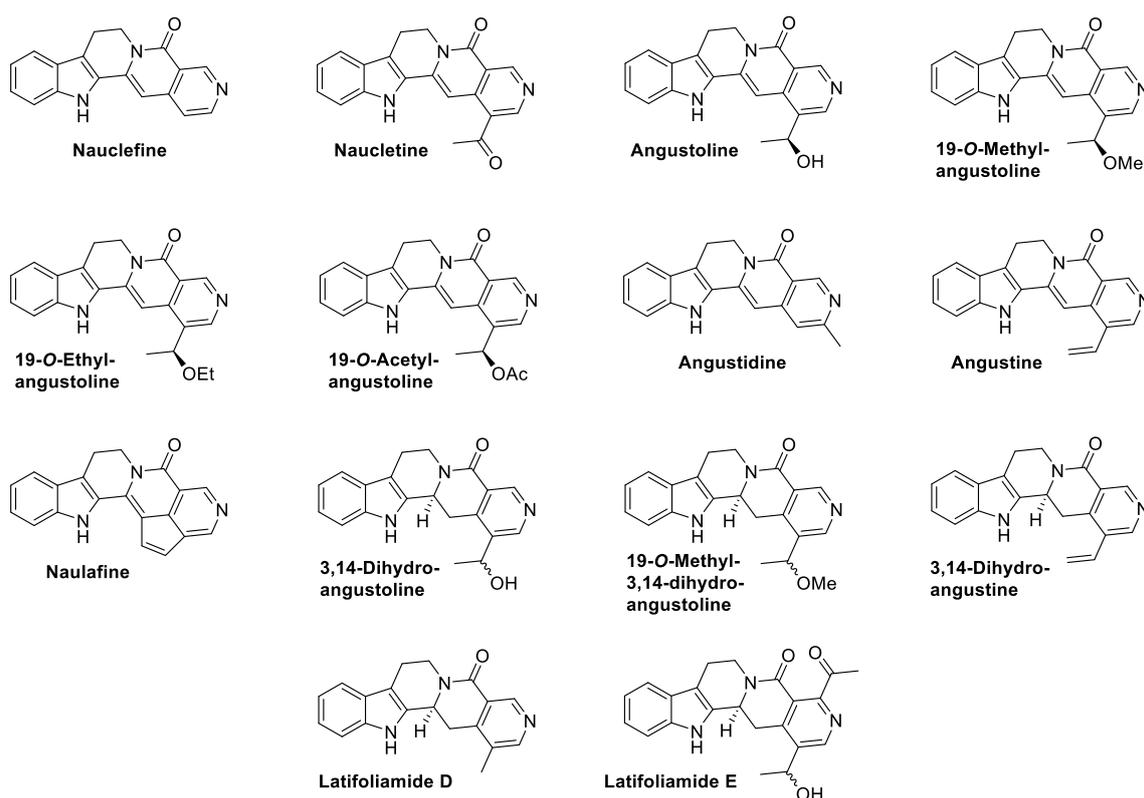


Figure 7. Structure of nauclefine-based indolo[2,3-a]quinolizidine derivatives isolated from African *Nauclea* species.

Alternatively, strictosamide-based indolo[2,3-a]quinolizidines can be formed upon cyclization of strictosidine derivatives. Strictosamide itself has been frequently isolated from various parts

of *N. latifolia* (Hotellier et al., 1977; Brown et al., 1977; Shigemori et al., 2003; Ata et al., 2009; Boumendjel et al., 2013) and *N. pobeguinii* (Zeches et al., 1985; Xu et al., 2012; Kuete et al., 2015) through alcoholic extraction, sometimes in very high yields (Figure 8). Indeed, amounts up to 1.7% for *N. latifolia* (Abreu and Pereira, 2001b) and 0.85% for *N. pobeguinii* (Mesia et al., 2010) have been measured, and the compound could thus occupy a key place in the pharmacological properties of traditional preparations. Close analogues were also reported from *Nauclea* species: 21-*O*-methylstrictosamide, 21-*O*-ethylstrictosamide (*N. latifolia*; Abreu and Pereira, 2001b), 10-hydroxystRICTOSAMIDE, naucleamide C (*N. latifolia*; Shigemori et al., 2003) and 3 α ,5 α -tetrahydrodeoxycordifoline lactam (*N. pobeguunii* and *N. diderrichii*; Lamidi et al., 2005; Xu et al., 2012). Several 16,17-dihydro derivatives were discovered, such as naucleofficine D (*N. pobeguunii*; Xu et al., 2012), latifoliamides B and C (*N. latifolia*; Agomuoh et al., 2013), or nauclefolinine (*N. latifolia*; Ngnokam et al., 2003), and a pyridine glucosyl analogue was identified as naucleamide F (*N. latifolia*; Kakuguchi et al., 2009; Ata et al., 2009). Finally, four compounds are carbonyl or carboxyl derivatives of strictosamide: naucleidinal (*N. latifolia* and *N. pobeguunii*; Hotellier et al., 1980; Abreu and Pereira, 2001b; Xu et al., 2012), 19-*epi*-naucleidinal (*N. latifolia*; Hotellier et al., 1980; Abreu and Pereira, 2001b), naucleidinic acid and magniflorine (*N. pobeguunii*; Xu et al., 2012).

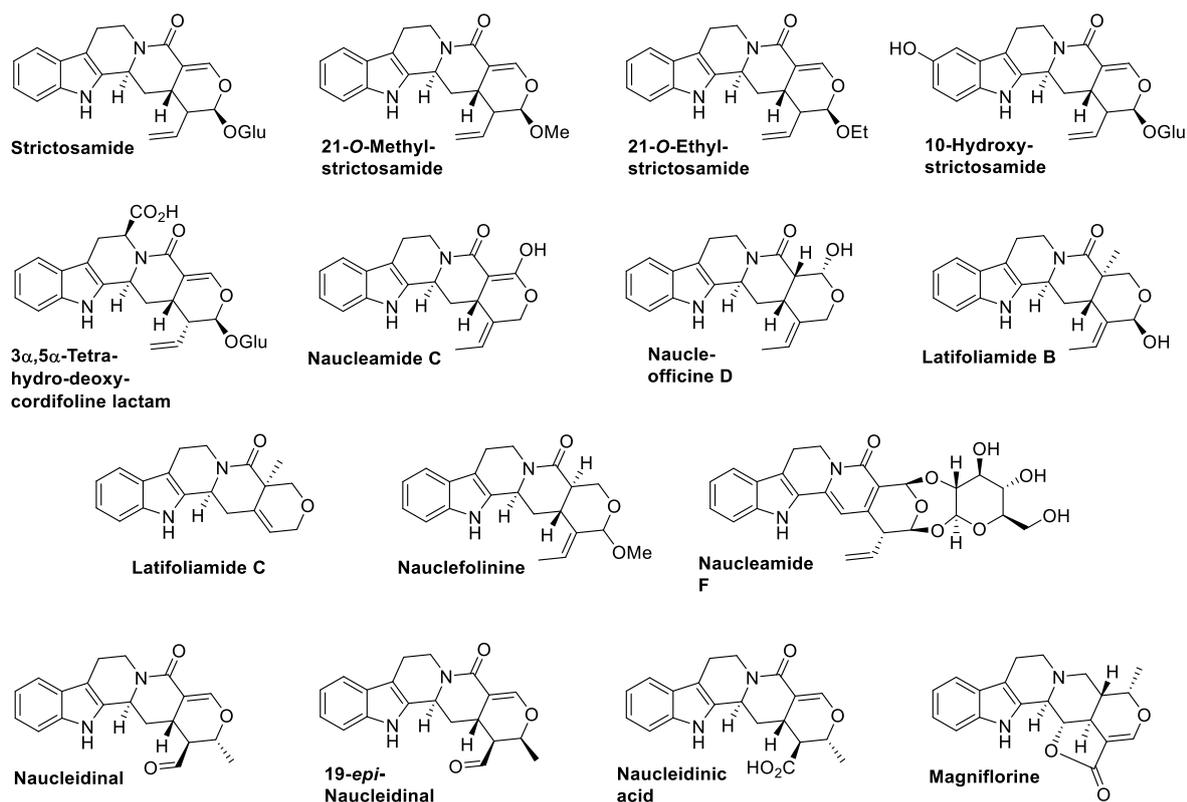


Figure 8. Structure of strictosamide-based indolo[2,3-a]quinolizidine derivatives isolated from African *Nauclea* species.

Besides the two aforementioned subfamilies of indolo[2,3-a]quinolizidines, eight additional analogues with various structures have been described to date (Figure 9): naucleamide A, B, D, E (*N. latifolia*; Shigemori et al., 2003; Ata et al., 2009; Boumendjel et al., 2013), latifoliamide A (*N. latifolia*; Agomuoh et al., 2013), nauclefitine, nauclefidine and nauclequiniine (*N. pobeginii*; Mao et al., 1984; Anam, 1997).

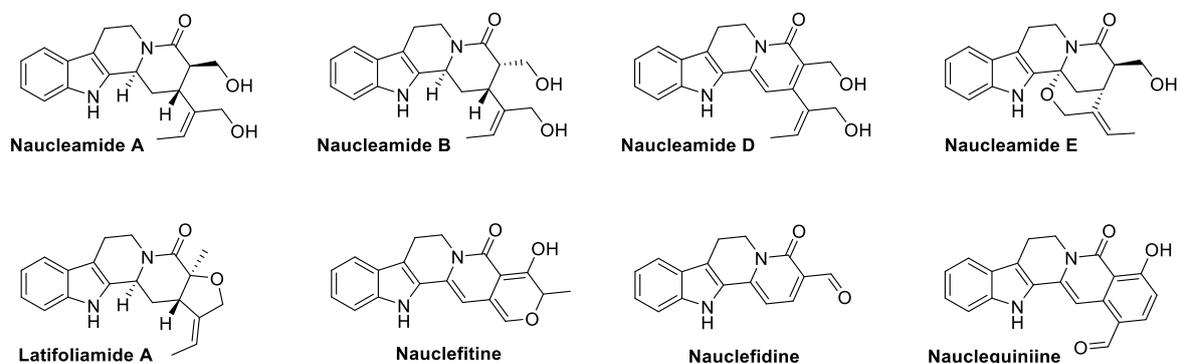


Figure 9. Structure of other indolo[2,3-a]quinolizidine derivatives isolated from African *Nauclea* species.

Several metabolites from African *Nauclea* were identified as seven-membered ring counterparts to indolo[2,3-a]quinolizidines. Among them, the cadambine and naufoline subclasses appear as closely related to the strictosamide-based and naufoline-based indolo[2,3-a]quinolizidines, respectively (Figure 10). Four pyrane-based compounds have been reported so far from African species of genus: cadambine (*N. latifolia*; Hotellier et al., 1979), 3 α -dihydrocadambine (*N. latifolia* and *N. diderrichii*; Dmitrienko et al., 1974a; MacLean et al., 1976; Hotellier et al., 1979), cadambine acid (*N. diderrichii*; Lamidi et al., 2005) and ND-370 (*N. diderrichii*; MacLean et al., 1976). On the other hand, six pyridine-based molecules are known as *Nauclea* constituents: naufoline (*N. latifolia* and *N. pobeguinii*; Hotellier et al., 1976, 1979; Zeches et al., 1985), 16-carbomethoxynaufoline, 18,19-dihydro-16-carbomethoxynaufoline (*N. diderrichii*; Richard et al., 1992), nauclechine (*N. diderrichii* and *N. latifolia*; Murray et al., 1972; Hotellier et al., 1981), descarbomethoxynauclechine (*N. latifolia*; Hotellier et al., 1976; Boumendjel et al., 2013) and nauclefoline (*N. latifolia*; Hotellier et al., 1981).

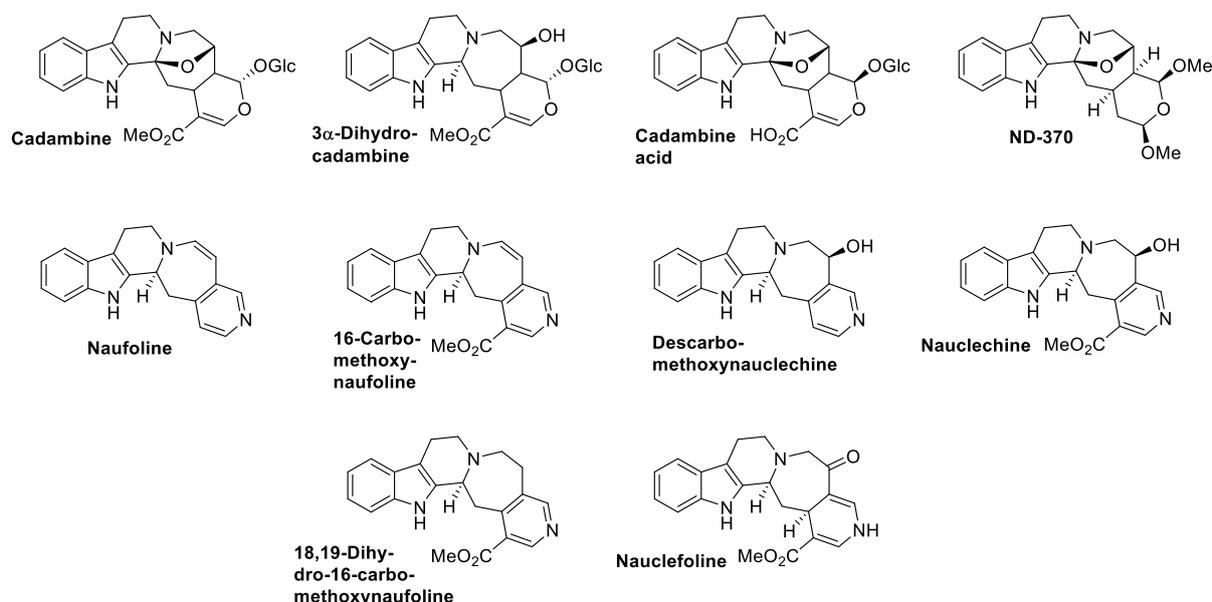


Figure 10. Structure of indolo[2,3-a]pyrido[1,2-a]azepine derivatives isolated from African *Nauclea* species.

Finally, four additional compounds are unusual indole alkaloids isolated from *N. diderrichii* (Figure 11), such as the oxazole-based naucleonine and naucleonidine, the seven-membered ring nauclederine and the macrocyclic nauclexine (Murray et al., 1972; Dmitrienko et al., 1974b; MacLean et al., 1976).

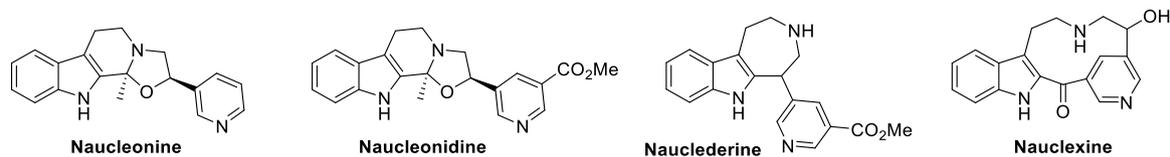


Figure 11. Structure of other indole-based derivatives isolated from the genus *Nauclea*.

Finally, tramadol, a synthetic alkaloid known as strong analgesic, has been extracted by Boumendjel et al. from *N. latifolia* in 2013 (Figure 12). Following this discovery, a controversy emerged about the origin of the presence of tramadol in the plant roots, i.e. natural vs. anthropogenic. After several contradictory studies published these past three years, the debate remains open (Kusari et al., 2014, 2016; Lecerf-Schmidt et al., 2015; Romek et al., 2015; Boucherle et al., 2016).

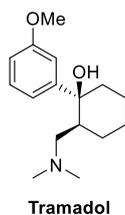


Figure 12. Structure of tramadol, isolated from the roots of *N. latifolia*.

4.3. Phenolic Compounds

Six phenolics have been isolated from the three main species of African *Nauclea* (Figure 13): antiarol (*N. diderrichii*; MacLean and Murray, 1972b), kelampayoside A (*N. pobeguinii*; Xu et al., 2012), *p*-coumaric acid, resveratrol, resveratrol glucoside (*N. pobeguinii*; Kuete et al., 2015) and scopoletin (*N. latifolia*; Abreu and Pereira, 2001b).

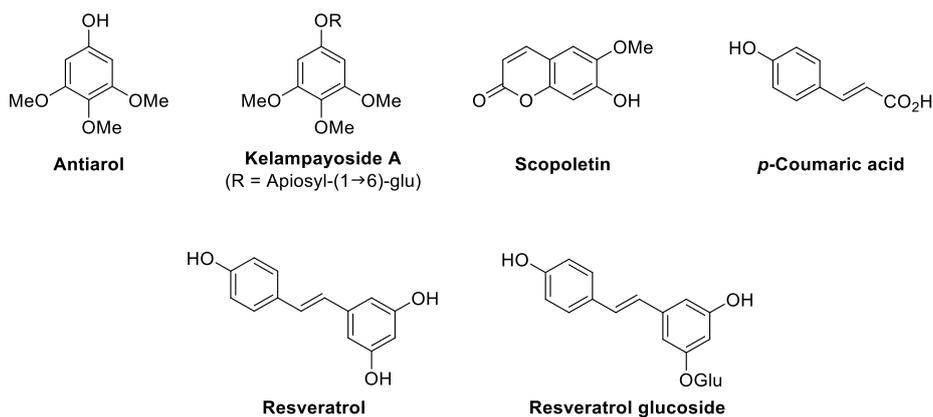


Figure 13. Structure of phenolic compounds isolated from African *Nauclea* species.

5. Pharmacological activities

5.1. Anti-infective

5.1.1. Anti-parasite

Based on their traditional uses against malaria *N. latifolia* and *N. pobeguinii* have been evaluated as antiplasmodial (Table 14). The first report of antimalarial activity of *N. latifolia* stem and roots aqueous extracts on *Plasmodium falciparum* was published in 1998 by Benoit-Vical et al. This activity was later confirmed by other studies using aqueous, alcoholic or hydro-alcoholic extracts of stem bark, roots or leaves (Udobre et al., 2013a; 2013b; Zirihi et al., 2005; Etebong et al., 2014; Onyesom et al., 2015; Dibua et al., 2013; Adebajo et al., 2014; for a review see Boucherle et al., 2016). Hydro-alcoholic extracts of *N. pobeguinii* stem bark also presented antiplasmodial activity. These pharmacological activities, as mentioned previously, led to the development of two improved traditional medicines in D.R. Congo and Nigeria using *N. pobeguinii* and *N. latifolia* extracts respectively (Mesia et al., 2005; 2010; 2012a; 2012b; Pieters, 2008; Gamaniël, 2009).

The antihelminthic efficacy of *N. latifolia* was studied with various approaches and several models (Table 14). In sheep with acute or sub-acute parasitic gastro-enteritis due to infection

by mixed nematode species, oral administration of extracts significantly reduced faecal egg counts for both aqueous stem bark and ethanolic leaf extracts at 500 mg/kg compare to untraited control (Ademola et al., 2006) or with an efficacy at 1600 mg/kg comparable to albendazole (5 mg/kg) (Onyeyili et al., 2001). The larvicidal efficacy of hot, cold water and ethanolic extracts on *Heligmosomodes bakeri* larvae at 5000 µg/ml was assessed. The mortality rate of L₁ larvae was 77, 89 and 74% for hot, cold water and ethanolic extracts respectively while for L₂ larvae, 83, 78 and 83% mortality rate were observed (Wabo Poné et al., 2012). Furthermore, aqueous extracts of *N. latifolia* leaves paralyzed *T. columbriformis* L₃ larvae with EC₅₀ value of 0.52 mg/ml at 24 h (Asuzu and Njoku, 1996). Helminth glutathione-S-transferases (GSTs) are potential targets for antihelmintic compounds since GST could protect the parasite against an immune response from its host. Stem bark hydro-methanolic extract contained inhibitors against recombinant *Ascaris* and *Onchocerca* GSTs with IC₅₀ of 15 and 28 mg/mL respectively (Fakae et al., 2000).

The anti-parasitic activity of *N. latifolia* on various other parasites (i.e. trypanosome, leishmania and amoeba) was also investigated. Stem bark and wood extracts were evaluated on amastigote and promastigote forms of *Leishmania major*. A methanolic extract of stem bark was found to be active only on the latter form (17% survival) (Ahua et al., 2007). Dichloromethane extract reduced survival of both forms (15% survival for promastigote form and 19% for amastigote form) when the control compound Amphotericin B was about 10 times more potent (1% and 2% survival for promastigote and amastigote forms respectively) but presented a higher toxicity on macrophage survival (60% compare to 88% for *N. latifolia* extract).

In mice experimentally infected with *Trypanosoma brucei brucei*, the root bark ethanolic extract was evaluated and found to decrease the level of parasitaemia in a dose dependent manner (Madubunyi, 1996). The trypanosomes were completely eradicated at 6th day after

treatment at a dose range of 40 to 100 mg/kg. Studying methanolic extracts of stem bark and leaves, Olanrewaju et al. were not able to show trypanocidal effect (Olanrewaju et al., 2014).

The traditional use of *Nauclea latifolia* as antidiarrheal led to its evaluation on *Entamoeba histolytica* growth. The root bark aqueous extract exhibited antiameobic activity with minimum amoebicidal concentrations $\leq 5 \mu\text{g/ml}$ (Tona et al., 2000; 2009).

Table 14. Reported antiparasite activities of African *Nauclea* species.

<i>Properties</i>	<i>Species</i>	<i>Plant parts</i>	<i>Extracts</i>	<i>Reference</i>
Anti-plasmodial	<i>N. latifolia</i>	S, R	Aq (m, d)	Benoit-Vical et al., 1998
	<i>N. latifolia</i>	SB	EtOH (d)	Zirihi et al., 2005
	<i>N. latifolia</i>	SB	MeOH (m)	Udobre et al., 2013a
	<i>N. latifolia</i>	L	MeOH (m)	Udobre et al., 2013b
	<i>N. latifolia</i>	L	Aq (d)	Dibua et al., 2013
	<i>N. latifolia</i>	R	EtOH : H ₂ O (70 : 30) (m)	Adebajo et al., 2014
	<i>N. latifolia</i>	L	EtOH : H ₂ O (70 : 30) (m)	Ettebong et al., 2014
	<i>N. latifolia</i>	L	Aq (d)	Onyesom et al., 2015
	<i>N. pobeguinii</i>	SB	MeOH : H ₂ O (80 : 20) (m)	Mesia et al., 2005; 2010; 2012a; 2012b
<i>N. pobeguinii</i>	SB	EtOH : H ₂ O (80 : 20)	Pieters, 2008	
Anti-helminthic	<i>N. latifolia</i>	L	Aq	Asuzu and Njoku, 1996
	<i>N. latifolia</i>	L	MeOH : H ₂ O (50 : 50) (m)	Fakae et al., 2000
	<i>N. latifolia</i>	L	Aq (d), EtOH (d)	Ademola et al., 2006
	<i>N. latifolia</i>	SB	Aq (d)	Onyeyili et al., 2001
	<i>N. latifolia</i>	SB	Aq (d and m), EtOH	Wabo Poné et al., 2012
Anti-leishmanial	<i>N. latifolia</i>	SB	CH ₂ Cl ₂ (m)	Ahua et al., 2007
Trypanocidal	<i>N. latifolia</i>	RB	EtOH : H ₂ O (70 : 30) (d)	Madubunyi, 1996
No trypanocidal effect	<i>N. latifolia</i>	SB, L	MeOH (m)	Olanrewaju et al., 2014
Anti-amoebic	<i>N. latifolia</i>	RB	<i>n</i> -BuOH (soluble fraction)	Tona et al., 2000; 2009

Bark (B), Stem Bark (SB), Root (R), Root Bark (RB), Stem (S), Leaf (L), Aq (Aqueous), m (maceration), d (decoction).

5.1.2. Antimicrobial

Antimicrobial activity of *N. latifolia* have been extensively described since decades. Both aerial parts (i.e. fruits, leaves and stem bark) and roots were extracted using different organic solvents or water and their antimicrobial activities on various bacteria or fungi strains were tested (Table 15). The available data present few conclusions due to conflicting results by different authors. However, the key points emerging are: (1) an overall good anti-bacterial activities of alcoholic extracts of all part of the plant against a broad spectrum of pathogens including gram negative or positive bacteria and fungi, (2) a poor efficiency of extracts using nonpolar solvents (e.g. alkanes), and (3) very contrasted results for aqueous extracts which are the most described mode of intake for traditional uses. A rationalization of the antimicrobial activities is so very difficult and further complicated by the lack of standardization in antimicrobial evaluations and the absence of a common reference as positive control. *N. pobeguinii* root, bark and leaf methanolic extracts were evaluated as antimicrobial. Both plant parts extracts were found inhibitors of bacterial growth on several pathogen bacteria (Njimoh et al., 2015, Seukep et al., 2016). Moreover a synergistic effect to various usual antibiotics was shown, thereby validating their use during treatment of resistant bacteria strains.

Table 15. Reported antimicrobial activities of African *Nauclea* species.

<i>Plant parts</i>	<i>Extract</i>	<i>S. aureus</i>	<i>S. pneumoniae</i>	<i>B. cereus</i>	<i>S. dysenteriae</i>	<i>B. subtilis</i>	<i>S. varidans</i>	<i>S. sonneri</i>	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>P. aeruginosa</i>	<i>S. parathypi</i>	<i>S. flexneri</i>	<i>S. typhi</i>	<i>Salmonella sp</i>	<i>A. niger</i>	<i>C. albicans</i>	<i>P. notatum</i>	<i>References</i>
<i>N. latifolia</i>																			
Stem Bark	Alkanes	-	-	+	+/-				-	-	-		-	-		-	-		Anowi et al., 2012a; 2012b ; Tekwu et al., 2012; Abiodun et al., 2007; Osadebe et al., 2010; Maitera et al., 2011; Kubmarawa et al., 2007; El-Mahmood et al., 2008
	CHCl ₃	+			+	+	+		+	+	+					-	+/-	-	
	EA	+		+	+	+			+/-	+	+		-	+		-	+		
	EtOH	+/-			+	+			+	+	-						+		
	MeOH	+	+	+	+	-	-		+/-	+/-	+	+	+	+		-	+/-	-	
Aq	+/-	-			+/-				+/-	+	-								
Unripe fruit	Alkanes	-				+			+	+	-			+					Fadipe et al., 2013
	MeOH	-				-			+	+	+			+					
Ripe fruit	Alkanes	-				-			-	-	+			+					Fadipe et al., 2013
	MeOH	+				+			-	+	+			+					
Leaf	Alkanes	+/-	-	+	+/-				-	-	+		+	+/-			+		Anowi et al., 2012b; Ogueke et al., 2011; Tekwu et al., 2012; Okiei et al., 2011; Maitera et al., 2011; Musa et al., 2011; Fagbohun et al., 2010; Okwori et al., 2008; Osadebe et al., 2010; El-Mahmood et al., 2008
	CHCl ₃	+							-		+			+/-					
	EA	+/-		+	+	+			+	+	+		+	+		+	+		
	EtOH	+			+				+/-	+	+/-			+/-					
	MeOH	+	+	+	+	+		-	+	+	+	+	+	+	-		+		
Aq	+/-	+			+/-			-	+/-	+	+/-			+/-	+				
Root	CHCl ₃	+					+		+		+			+/-					Lagnika et al., 2011; Deeni and Hussain, 1991; El-Mahmood et al., 2008, Okwori et al., 2008; Okechukwu et al., 2015; Okoli and Iroegbu 2004
	Et ₂ O	+									+			-					
	EtOH	+			+	+			+/-	+	+/-				+	+			
	MeOH	+					+		+/-		+/-			+					
	Aq	+/-			+	-	+		+/-	+	+/-			+/-					
<i>N. pobeguini</i>																			
Bark	MeOH								+/-	-	-								Seukep et al., 2016
Leaf	MeOH								-	-	-								Seukep et al., 2016
Root	MeOH								+	+				+			+		Njimoh et al., 2015

Aq (Aqueous); EA (Ethylacetate); +: antimicrobial activity; -: no antimicrobial activity; +/-: Activity is different among the different strains tested.

5.1.3. Miscellaneous

Molluscicidal activity of *N. latifolia* bark methanol and aqueous extract was assessed using a survival test on *Lymnae natalensis* (Kela et al., 1989a; 1989b), as this snail is the intermediate host of *Fasciola hepatica* (Table 16). Only the water extract exhibited an activity with a LC₅₀ of 42 mg/L.

The folk medicinal use of *N. latifolia* against yellow fever and jaundice had conducted Donalisio et al. to evaluate the antiviral activity of a dichloromethane/methanol root bark extracts (Donalisio et al., 2013). An inhibition was observed for both aciclovir sensitive (IC₅₀ = 5.4 µg/ml) and aciclovir resistant (IC₅₀ = 7.8 µg/ml) strains on the HSV-2 model chosen.

Table 16. Reported miscellaneous anti-infective activities of African *Nauclea* species.

<i>Properties</i>	<i>Species</i>	<i>Plant parts</i>	<i>Extracts</i>	<i>Reference</i>
Molluscicidal	<i>N. latifolia</i>	B	MeOH (m), Aq, (m)	Kela et al., 1989a; 1989b
Anti-viral	<i>N. latifolia</i>	RB	MeOH : CH ₂ Cl ₂ (50 : 50) (m)	Donalisio et al., 2013

Bark (B), Root Bark (RB), Aq (Aqueous), m (maceration).

5.2. Digestive

Digestive activities of *N. latifolia* were reported through antidiarrheal and anti-ulcer evaluations (Table 17). Hydro-alcoholic root bark extract of *N. latifolia* was found to exert antidiarrheal activity on castor oil-induced diarrhea (Owolabi et al., 2010). Balogun et al. published several studies on gastric protection of *N. latifolia* extracts using indomethacin-induced ulcer rat model. A significant augmentation of ulcer protection from 67% at 170 mg/kg to 91% at 510 mg/kg was reported for aqueous leaf extract while cimetidine used as control at 100 mg/kg presented 76% of protection (Balogun et al., 2013). Effects of aqueous and methanolic leaf extracts on

gastric acid secretion was also investigated and a significantly and dose dependently decrease was observed. The total gastric acid content was lowered from 9.8 μ Eq HCl/100g of body weight and 6.1 at 400 mg/kg for methanol and water extract respectively (control: cimetidine 5.6 μ Eq HCl/100g of body weight at 100 mg/kg) (Balogun et al., 2014; 2015). The hydro-alcoholic extract did not exhibit any protective effects on aspirin-induced ulcer in rats (Orole et al., 2013). Stem bark hydro-methanolic extract anti-ulcer activity was also investigated in histamine and aspirin induced-ulcer models in rats. This extract significantly increased ulcer tolerance rate compared to controls at 50mg/kg but was found ineffective at 100 mg/kg (Alaribe et al., 2014). The same extract was found potent on *Helicobacter pylori* with MIC of 25 mg/mL (amoxicillin: MIC = 3.1 mg/mL) (Alaribe et al., 2014).

Table 17. Reported digestive activities of African *Nauclea* species.

<i>Properties</i>	<i>Species</i>	<i>Plant parts</i>	<i>Extracts</i>	<i>Reference</i>
Anti-diarrheic	<i>N. latifolia</i>	RB	EtOH : H ₂ O (70 : 30) (m)	Owolabi et al., 2010
Anti-ulcer	<i>N. latifolia</i>	L	Aq (i)	Balogun et al., 2013; 2014
	<i>N. latifolia</i>	SB	MeOH : H ₂ O (50 : 50) (d)	Alaribe et al., 2014
	<i>N. latifolia</i>	L	MeOH (d)	Balogun et al., 2015
No anti-ulcer effect	<i>N. latifolia</i>	L	MeOH : H ₂ O (50 : 50) (m)	Orole et al., 2013

Root Bark (RB), Stem Bark (SB), Leaf (L), Aq (Aqueous), m (maceration), d (decoction), i (infusion).

5.3. Pain and other neurologic uses

Many studies have been conducted on neurologic effects of *N. latifolia* (Table 18). Using animal models, analgesic, anticonvulsivant, anxiolytic, sedative, antidepressant and myorelaxant activities were described. The first analgesic activity of an extract of *N. latifolia* was reported by Okiemy-Andissa et al. in 2004 on acetic acid-induced writhing and hot plate mice models

using aqueous and hydro-ethanolic extracts of aerial parts. Same evaluations were conducted with methanolic extract of stem bark (Otimenyin and Uguru, 2007) or with aqueous macerate of root bark (Abbah et al., 2010) and also demonstrated analgesic effect. Total alkaloids extracts of root and leaf were found moderately active on acetic acid-induced writhing mice model (Badiaga, 2011). Besides, studies on other neurologic properties of *N. latifolia* were conducted by Taiwe and colleagues. They first assessed anticonvulsant, anxiolytic and sedative effects on mice of aqueous root extract (Ngo Bum et al., 2009). Other evaluations on the same type of extract on mice confirmed anxiolytic (Taiwe et al., 2010) and analgesic (Taiwe et al., 2011; 2014) effects and also showed myorelaxant and antidepressant (Taiwe et al., 2010) activities. Studying ethanolic extract of fruits in rat model, Shamoun et al. demonstrated sedative, anticonvulsant and anxiolytic properties (Shamoun et al., 2014). However, the anxiolytic effect of the same kind of extract was infirmed using mice model (Arome et al., 2014). Sedative properties of aqueous macerate on mice and rats have also been reported (Amos et al., 2005). Furthermore, methanolic leaf and root extracts of *N. latifolia* were evaluated and found to possess interesting pharmacological actions on purinergic neurotransmission using a rat bladder model (Udoh, 1995).

Table 18. Reported neuropharmacological activities of African *Nauclea* species.

<i>Properties</i>	<i>Species</i>	<i>Plant parts</i>	<i>Extracts</i>	<i>Reference</i>
Analgesic	<i>N. latifolia</i>	AP	EtOH : H ₂ O (m), Aq (m)	Okiemy-Andissa et al., 2004
	<i>N. latifolia</i>	SB	MeOH	Otimenyin and Uguru, 2007
	<i>N. latifolia</i>	RB	Aq (m)	Abbah et al., 2010
	<i>N. latifolia</i>	R, L, B	Alk	Badiaga, 2011
	<i>N. latifolia</i>	R	Aq (m)	Taiwe et al., 2011

	<i>N. latifolia</i>	R	Acetone : H ₂ O (70 : 30) (m)	Taiwe et al., 2014
Anticonvulsivant	<i>N. latifolia</i>	R	Aq (m)	Ngo Bum et al., 2009
Anxiolytic and sedative	<i>N. latifolia</i>	RB	Aq (m)	Amos et al., 2005
	<i>N. latifolia</i>	R	Aq (m)	Taiwe et al., 2010; Ngo Bum et al., 2009
	<i>N. latifolia</i>	F	EtOH	Shamoun et al., 2014
No anxiolytic effect	<i>N. latifolia</i>	F	EtOH (m)	Arome et al., 2014
Myorelaxant	<i>N. latifolia</i>	R	Aq (m)	Taiwe et al., 2010
	<i>N. latifolia</i>	F	EtOH	Shamoun et al., 2014
Antidepressant	<i>N. latifolia</i>	R	Aq (m)	Taiwe et al., 2010
Purinergic neurotransmission	<i>N. latifolia</i>	R, L	MeOH (d)	Udoh, 1995

Stem Bark (SB), Root (R), Aerial parts (AP), Root Bark (RB), Leaf (L), Fruit (F), Aq (Aqueous), m (maceration), d (decoction), Alk (Total alkaloids).

5.4. Metabolic disorders

Metabolic disease prevalences are increasing in Africa. In order to rationalize traditional therapeutic uses of *Nauclea* species for these indications, several authors have conducted studies especially on hypertension- and diabetes-related effects of these plants (Table 19). Methanolic extracts of leaf and root of *N. latifolia* presented opposite effects on the cardiovascular systems of rats and rabbits. While leaf extract potently reduced both mean arterial blood pressure in rats from 122 to 95 mm Hg and rabbit heart rate, root extract was found hypertensive *via* adrenoreceptor stimulation (Udoh and Lot, 1998). 10 mg/kg of the ethanolic root extract also reduced the mean arterial pressure from 116 to 100 mm Hg and 157 to 72 mm Hg on normotensive and hypertensive rats respectively while concomitantly reducing the heart rate from 365 to 280 beats/min and from 550 to 120 beats/min respectively (Nworgu et al., 2008). The hypotensive effect was confirmed on normotensive rabbits using sub-fractions

of the ethanolic root extract (Nworgu et al., 2009). Odey et al. evaluated body and organ weight changes of hypertensive rats fed with ethanolic root or stem bark extracts of *N. latifolia*. A significant decrease in heart and liver weight of rats treated with 150 mg/kg of any of the extracts was associated with significant increase in the body weight (Odey et al., 2012a). A 40% relaxation on pre-contracted thoracic aorta was elsewhere reported on rats treated with the ethanolic leaf extract (Akpanabiatu et al., 2005a).

Since extracts of *N. latifolia* are traditionally used for the treatment of diabetes, several studies demonstrated antidiabetic effects using murine models. An aqueous extract of the leaves was found to significantly lower the glucose level in alloxan-induced diabetic rats by 45% (Gidado et al., 2005), and the fasting blood glucose (FBG) by 32% of the streptozotocin-induced diabetic rats (Gidado et al., 2008). In the latter model, hexanic extract was inactive while ethanolic leaf extract presented a similar potency to the aqueous extract (Gidado et al., 2008) and significantly reduced FBG levels in a dose-independent manner (Gidado et al., 2009). However, other authors reported inactivity of ethanolic extract on blood glucose level using the same model (Effiong et al., 2013a). Ethanolic leaf extract was also evaluated on non-diabetic rats. After both oral and intraperitoneal glucose loads, it inhibited the increase of glucose level and both maltase and sucrase activities *in vitro* but not *in vivo*, suggesting a similar mechanism to that of glibenclamide, i.e. an increase of insulin release from pancreatic β -cells (Gidado et al., 2012). In acute study and prolonged treatment, oral administration of an ethanolic root extract (450 mg/kg) caused a significant reduction in FBG levels with values similar to the reference glibenclamide (10 mg/kg) (Antia and Okokon 2014). Effects of root and stem extracts on diabetic pregnant rats were evaluated. If a butanolic extract decreased glycaemia in streptozotocin-induced diabetic pregnant rats, an ethanolic extract was ineffective and both of them were not active on normal pregnant rats (Yessoufou et al., 2013). Aqueous root extract of *N. latifolia* and *Daniella oliveri* (1:1, w:w) was investigated on normoglycaemic and alloxan-

induced diabetic rats and presented a significant lowering of blood sugar level in diabetic rats from 302 mg/dL to 119 mg/dL but did not show any effect in normoglycaemic rats (Iwueke and Nwodo, 2008). α -amylase inhibition using methanolic stem bark extract of *N. diderrichii* was assessed. It was found as a potent inhibitor with IC_{50} of 248 μ g/mL, comparable to reference α -amylase inhibitor acarbose ($IC_{50} = 177 \mu$ g/mL) (Ogbole et al., 2016). Similar results were obtained by Agnani et al. on aqueous extracts of bark and leaf (Agnani et al., 2016). The later showed a 60-fold better potency than acarbose. During the same evaluation aqueous extracts of bark of *N. pobeguinii* also presented a good inhibition of α -amylase (Agnani et al., 2016).

Otherwise, *N. latifolia* extracts administration also conducted to changes in lipid metabolism. Hence, total cholesterol (TC) and high density lipoprotein (HDL) levels significantly decreased and low density lipoprotein (LDL) and triacylglycerol (TG) levels raised after feeding normal rats with an aqueous stem extract (Arise et al., 2012). Different results were obtained when ethanol leaf extract and its sub-fractions were evaluated on alloxan-induced diabetic rats: for all sub-fraction-treated groups, TC and HDL levels also decreased and no significant change was observed for TG. Very low density lipoprotein (VLDL) level decreased upon treatment with methanol, butanol and ethyl acetate subfraction (Edet et al., 2011). Total cholesterol was lowered to non-hypertensive control values by both stem and root ethanolic extracts after oral administration on hypertensive rats (Odey et al., 2012b). No significant change was observed for the TG, LDL and VLDL levels while treatment increased HDL levels. Ethanolic extract of the leaf re-extracted in cold water did not present significant changes in the lipid profile of the experimental animals fed with 10% coconut oil meal compared to the controls (Akpanabiatu et al., 2005a). Using a Poloxamer 407 induced hypercholesterolemic rat model, root extracts (crude, ethyl acetate and butanol) were evaluated on lipid metabolism (Effah, 2014). When extracts were administrated before induction of hypercholesterolemia, they provoked a

reduction of TC and TG. The groups treated with aqueous and ethyl acetate extracts also presented a decrease of LDL levels. In a curative treatment, all the groups showed significant increase in the HDL level, ethyl acetate and butanol extract were able to lower TG while only the ethyl acetate extract provoked a decrease in TC. *N. latifolia* methanolic leaf extract was evaluated on rats treated with ciprofloxacin showing a hypolipidaemic effect associated to an anti-lipid peroxidative efficiency (Chinedu et al., 2013). Cholesterolemia was measured on rats fed with crude fruits of *N. latifolia*. The supplementation of total alimentation induced hypocholesterolemic effect in a dose-dependent manner (James and Ugbede, 2011).

The hormonal effects of *N. latifolia* roots extracts were explored. An aqueous infusion was evaluated on rats with cyproteron acetate-caused testis failure which is a traditional indication of the plant. Extract administration conducted to an increase of testis weight from 1% for control to 13% and allowed a regeneration of germinal function of testis, unlike the control group (Rukundo, 2007). Based on these results, other authors studied the influence of administration of a *N. latifolia* aqueous extract both on fertility rate of male and female rats, and on body weight gain of young rats from treated parents. The treatment of female rats was ineffective on both parameters while treatment of male rats led to an augmentation of the fertility rate as compared to control (40% and 60% respectively) and an increase of body weight gain of newborn rats perceptible until day 25 after birth (Ishimwe, 2008).

The use of *N. latifolia* by traditional healers to stop pre-term labor has been reported. The ethanolic extract of the roots was then evaluated on agonist-induced contractions of uterine smooth muscles in non-pregnant female rats and clearly indicated an anti-abortifacient property since a reduction of oxytocin, acetylcholine and ergometrine-induced uterine contractions was observed (Nworgu et al., 2010). A methanol extract of the roots of *N. latifolia* was screened in the yeast test-system to evaluate potential estrogenic properties. A promising activity was found and further investigations *in vivo* on ovariectomized Wistar rats were performed. *N. latifolia*

significantly increased vaginal epithelial height by 16% compared to untreated controls, suggesting an estrogenic activity (Njamen et al., 2008).

Table 19. Reported activities on metabolic disorders of African *Nauclea* species.

<i>Properties</i>	<i>Species</i>	<i>Plant parts</i>	<i>Extracts</i>	<i>Reference</i>
Anti-hypertensive	<i>N. latifolia</i>	L	MeOH	Udoh and Lot, 1998
	<i>N. latifolia</i>	L, R	EtOH (d)	Akpanabiatu et al., 2005a
	<i>N. latifolia</i>	R	EtOH (d), EtOH : H ₂ O (70 : 30) (d)	Nworgu et al., 2008; Nworgu et al., 2009
	<i>N. latifolia</i>	RB, SB	EtOH : H ₂ O (80 : 20) (m)	Odey et al., 2012a
Anti-diabetic	<i>N. latifolia</i>	L	Aq (m), EtOH (m)	Gidado et al., 2005; 2008
	<i>N. latifolia</i>	L	Aq (d)	Iwueke and Nwodo, 2008
	<i>N. latifolia</i>	L	EtOH (m)	Gigado et al., 2009; 2012; Effiong, 2013a
	<i>N. latifolia</i>	R, S	EtOH (m)	Yessoufou et al., 2013
	<i>N. latifolia</i>	L	EtOH : H ₂ O (50 : 50) (m)	Antia and Okokon, 2014
	<i>N. pobeguinii</i>	B	Aq (d)	Agnaniet et al., 2016
	<i>N. diderrichii</i>	L, B	Aq (m)	Agnaniet et al., 2016
	<i>N. diderrichii</i>	SB	MeOH (m)	Ogbole et al., 2016
Lipid metabolism	<i>N. latifolia</i>	L	EtOH (d)	Akpanabiatu et al., 2005a
	<i>N. latifolia</i>	L	EtOH (m)	Edet et al., 2011
	<i>N. latifolia</i>	F	MeOH (m)	James and Ugbede, 2011
	<i>N. latifolia</i>	S	Aq (m)	Arise et al., 2012
	<i>N. latifolia</i>	RB, SB	EtOH : H ₂ O (80 : 20) (d)	Odey et al., 2012b
	<i>N. latifolia</i>	L	MeOH	Chinedu et al., 2013
	<i>N. latifolia</i>	R	Aq (d)	Effah, 2014
	Hormonal activity	<i>N. latifolia</i>	R	Aq (i)
<i>N. latifolia</i>		R	EtOH, MeOH	Nworgu et al., 2010, Njamen et al., 2008

Bark (B), Stem Bark (SB), Root (R), Root Bark (RB), Stem (S), Leaf (L), Fruit (F), Aq (Aqueous), m (maceration), d (decoction), i (infusion).

5.5. Anti-inflammatory and antipyretic

Several anti-inflammatory and antipyretic assays have been performed using *N. latifolia* samples (Table 20). Anti-inflammatory effects of hydro-alcoholic root or leaf extracts of *N. latifolia* were evaluated on carrageenan-induced paw edema in rats. Both extracts significantly reduced inflammation with an effect similar to control (indometacine, 100 mg/kg) at 1000 mg/kg (Amouzoun et al., 2008). Similar anti-inflammatory results were obtained in egg albumine-induced oedema on rodent. A reduction of edema was obtained since 50 mg/kg using an aqueous extract of the root bark (Abbah et al.; 2010), while methanolic leaf and stem bark extracts exerted effects at 200 mg/kg and 150 mg/kg respectively (Otimenyin and Uguru, 2007; Osadebe et al., 2010). Three different studies also presented anti-pyretic activities in yeast-induced pyrexia on murine model. For aqueous extracts of the root bark, the maximal reduction in rectal temperatures was observed at a dose of 200 mg/kg at 90 min (Abbah et al., 2010). The tested dose for hydro-alcoholic leaf and root extracts was 1500 mg/kg and presented significant effect during 10 hours (Amouzoun et al., 2008). Fever reduction of the aqueous root extracts (at 4h, 80 mg/kg) was reported comparable to aspirin (300 mg/kg) (Taiwe et al., 2011).

Table 20. Reported anti-inflammatory and anti-pyretic activities of African *Nauclea* species.

<i>Species</i>	<i>Plant parts</i>	<i>Extracts</i>	<i>Reference</i>
<i>N. latifolia</i>	SB	MeOH	Otimenyin and Uguru, 2007
<i>N. latifolia</i>	L, R	MeOH : H ₂ O (50 : 50) (m)	Amouzoun et al., 2008
<i>N. latifolia</i>	L, SB	MeOH	Osadebe et al., 2010
<i>N. latifolia</i>	RB	Aq (m)	Abbah et al., 2010
<i>N. latifolia</i>	R	Aq (m)	Taiwe et al., 2011

Stem Bark (SB), Root (R), Root Bark (RB), Leaf (L), Aq (Aqueous), m (maceration).

5.6. Hepato-protective activity

Several authors presented studies on hepatoprotective activities in infective or toxicological liver damages contexts (Table 21). A ten days treatment with leaf decoction of *N. pobeguinii* (5 mg/kg) presented a hepatoprotective activity on CCl₄ intoxicated rats (Kadiri et al., 2007). The effects of the root bark ethanolic (100 mg/kg) and methanolic (300 mg/kg) extracts of *N. latifolia* on liver were also evaluated on the same model and presented hepatoprotective properties as they reduced the toxicity-induced elevation of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (AP) significantly (Madubunyi 1996, Udeh and Madubunyi, 2008), as well as the total and conjugated bilirubin levels for aqueous extract (100 mg/kg) (Yesufu et al., 2010). A similar effect was observed on acetaminophen intoxication of rats on AST, ALT and AP treated with methanolic leaf extract (100 mg/kg) (Nwaehujor et al., 2016). Furthermore, ethanolic leaf extract also exerted hepatoprotective effect on rats by (1) reduction of the activity of γ -glutamyl transferase if raised by other factors (at 170 mg/kg) (Akpanabiatu et al., 2005b) (2) AST, ALT levels diminution and restoration of normal proteinaemia in acetaminophen-treated rats (Effiong et al., 2013b; 2014).

Table 21. Reported hepatoprotective activities of African *Nauclea* species.

<i>Species</i>	<i>Plant parts</i>	<i>Extracts</i>	<i>Reference</i>
<i>N. pobeguunii</i>	B, L	MeOH (m)	Kuete et al., 2015
<i>N. latifolia</i>	RB	EtOH : H ₂ O (70 : 30) (d)	Madubunyi, 1996
<i>N. latifolia</i>	RB	MeOH	Udeh and Madubunyi, 2008
<i>N. latifolia</i>	RB	Aq (d)	Yesufu et al., 2010
<i>N. latifolia</i>	L	EtOH (m)	Effiong et al., 2013b; 2014
<i>N. latifolia</i>	L	MeOH (m)	Nwaehujor et al., 2016
<i>N. pobeguunii</i>	L	Aq (d)	Kadiri et al., 2007
<i>N. latifolia</i>	L	EtOH (d)	Akpanabiatu et al., 2005b

Bark (B), Stem Bark (SB), Root (R), Root Bark (RB), Stem (S), Leaf (L), Fruit (F), Aq (Aqueous), m (maceration), d (decoction).

5.7. Miscellaneous

Antioxidant activities on different parts of *N. latifolia* were described using different models. Free radical scavenging activity against 2,2-diphenyl-1-picrylhydrazyl (DPPH), hydroxyl, and superoxide anion radicals of a root methanolic extract was assessed by Awah et al. (Table 22). Indeed *N. latifolia* possesses antioxidant activity and lipid peroxidation inhibitory potency probably correlated with its phenolic and flavonoid components (Awah et al., 2012). An aqueous extract of the leaf and fruit also revealed an antioxidant potential with scavenging activity against DPPH with IC₅₀ of 20 mg/mL and 120 mg/mL respectively (Ayeleso et al., 2014). *N. latifolia* root and stem ethanolic extracts were tested on red blood cell model and showed a 50% increase of free radical-induced haemolysis time (Yessoufou et al., 2013). A study of oxidative stress and lipid peroxidation was performed using a model of alloxan-induced diabetic rats treated with an aqueous root extract. The extract (250 mg/kg) significantly reduced catalase activity (CAT), provoked changes in both malondialdehyde (MDA, a plasma and liver lipid peroxidation marker), and glutathione (GSH) but non-significantly reversed the superoxide dismutase (SOD) activity induced by diabetes (Iwueke et al., 2010). On a ciprofloxacin induced oxidative stress rat model, the methanolic leaf extract (1200 mg/kg) presented antilipid peroxidative potentials (Chinedu et al., 2013). *N. latifolia* alcoholic leaf extracts were tested against acetaminophen-induced hepatotoxicity in rats and showed antioxidant properties while the activities of CAT, glutathione peroxidase and SOD were decreased in treated rats vs. non treated ones (Effiong et al., 2013b; Nwaehujor et al., 2016). Using a model of mice infected by *P. berghei*, antioxidant effects (CAT, SOD and GSH system) of an aqueous extract of *N. latifolia* leaf were investigated. Not only an elimination of plasmodium was observed, but also an improvement of antioxidant defense even better than chloroquine-treated mice which means that the *N. latifolia* extract exhibits antioxidant effect on

its own (Onyesom et al., 2015). These results were not confirmed by Edagha *et al.* however who did not observe, using the same model, significant variations of antioxidant levels in the groups treated with ethanolic leaf extracts compared to control (Edagha et al., 2015).

The methanolic stem bark extract and its sub-fractions (100 mg/mL) were evaluated as cicatrizing agent. Both extracts except butanolic presented wound healing properties in tested rabbits with a complete sore recovery in 24 days using ethylacetate extract (30-35 days for control) (Udobre et al., 2012).

Yessoufou et al. also evaluated the immunomodulatory ability of an ethanolic macerate of root and stem of *N. latifolia*. Extracts were found as inhibitors of T cell proliferation activated by anti-CD3 antibody in a dose-dependent manner (Yessoufou et al., 2013).

Finally, bark and leaf methanolic macerates of *N. pobeguinii* led to IC₅₀ values around 30 µg/mL on various cancer cell lines (Kuete et al., 2015).

Table 22. Reported miscellaneous activities of African *Nauclea* species.

<i>Properties</i>	<i>Species</i>	<i>Plant parts</i>	<i>Extracts</i>	<i>Reference</i>
Antioxidant	<i>N. latifolia</i>	R	Aq (d)	Iwueke et al., 2010
	<i>N. latifolia</i>	R	MeOH (m)	Awah et al., 2012
	<i>N. latifolia</i>	R, S	EtOH (m)	Yessoufou et al., 2013
	<i>N. latifolia</i>	L	MeOH	Chinedu et al., 2013
	<i>N. latifolia</i>	L	EtOH (m)	Effiong et al., 2013b
	<i>N. latifolia</i>	L, F	Aq (d)	Ayeleso et al., 2014
	<i>N. latifolia</i>	L	Aq (d)	Onyesom et al., 2015
	<i>N. latifolia</i>	L	EtOH	Edagha, 2015
	<i>N. latifolia</i>	L	MeOH (m)	Nwaehujor et al., 2016
Wound healing	<i>N. latifolia</i>	SB	MeOH (m)	Udobre et al., 2012
Immunomodulation	<i>N. latifolia</i>	R, S	EtOH (m)	Yessoufou et al., 2013
Anti-proliferative	<i>N. pobeguinii</i>	B, L	MeOH (m)	Kuete et al., 2015

Stem Bark (SB), Root (R), Stem (S), Leaf (L), Fruit (F), Aq (Aqueous), m (maceration), d (decoction)

5.8. Toxicity studies

Many toxicity studies have been conducted in various models in order to assess safety of plant extracts. A study on hepatic enzymes (γ -glutamyl transferase, AST and ALT) on normal rats treated with an aqueous stem macerate showed a diminution of their liver activities simultaneously to an elevation in the plasma due to hepatotoxicity (Arise et al., 2012). An extensive toxicity evaluation was performed on rats and mice orally treated with an aqueous extract of *N. latifolia* stem bark. Single administration on mice allowed the determination of a $LD_{50} > 18$ g/kg body weight while sub-acute toxicity on several parameters was evaluated on rats. In blood, an elevation of platelets, erythrocytes and also eosinophils was observed associated with a decrease AST, ALT and creatinine. A high loss of water and depletion in sodium and potassium levels was observed in urine (Kouadio et al., 2014). Moreover, neither hepatotoxicity nor nephrotoxicity were measured for rats treated with the same kind of extract at 3.2 g/kg (Akinloye and Olaniyi, 2012). An aqueous leaf extract was similarly evaluated and presented an increase of AST, ALT and AP levels in serum associated with histopathological lesions of liver and kidney (Magili et al., 2014). Conducted on *Chinchilla* rabbit, a study of liver toxicity of an ethanolic crude extract of *N. latifolia* leaves, fruits, stem and root barks also demonstrated deleterious effects on hepatic functions since significant elevation of AST and ALT activities and hepatic injury were observed (Ogenyi et al., 2015). Liu *et al.* described genotoxic and clastogenic activity of a hydro-methanolic bark extract of *N. latifolia*, *N. pobeguinii* and *N. diderrichii*, the later being the most toxic (Liu et al., 2011). The authors linked this activity to the various saponins found in these extracts. Mesia et al. did not observe toxic effect after acute or prolonged treatment of 4 weeks of *N. pobeguinii* stem bark extract on mice. Moreover, no major lesions were found in the considered organs (Mesia et al., 2005; 2010). Evaluated on brine shrimp lethality assay, a methanolic macerate of stem bark of *N. diderrichii* showed a LC_{50} value of 1 μ g/mL. Ethanolic leaf extract administrated on gestational rat model

created histopathological alterations on neonatal kidneys and livers discouraging its use during pregnancy (Solomon et al., 2014a; 2014b). Bark and leaf methanolic macerates of *N. pobeguinii* led to IC₅₀ values around 30 µg/mL on various cancer cell lines (Kueté et al., 2015). An alkaloid rich extract of *N. latifolia* was able to interact *in vitro* with DNA of bacteria and mammalian cells as well as creating single-strand breaks in liver, kidney and blood cells *in vivo* (Traore et al., 2000). Cytotoxicity and growth inhibitory activity were evaluated on tadpoles of *Raniceps ranninus* and on radicle length of *Sorghum bicolor* seeds. A root bark methanolic extract induced 100% mortality at a dose of 200 µg/mL, while stem methanolic extract was less toxic with 33% of mortality at 400 µg/mL. Tested at 30 mg/mL, both stem bark and leaf extracts reduced the grow length of radicle by 99% and 95% respectively (Oise et al., 2014). During anti-inflammatory evaluation in rats, methanolic extracts of the stem bark of *N. latifolia* were reported to be highly toxic with a LD₅₀ of 850 mg/kg (Otimenyin and Uguru, 2007). Cardiotoxicity on isolated frog heart was also described for a hydro-alcoholic stem bark extracts (Gueye-Sanokho et al., 1993).

Table 22. Reported toxic activities of African *Nauclea* species.

<i>Species</i>	<i>Plant parts</i>	<i>Extracts</i>	<i>Reference</i>
<i>N. diderrichii</i>	SB	MeOH : H ₂ O (80 : 80) (m)	Liu et al., 2011
<i>N. diderrichii</i>	SB	MeOH (m)	Ogbole et al., 2016
<i>N. latifolia</i>	SB	EtOH : H ₂ O	Gueye-Sanokho et al., 1993
<i>N. latifolia</i>	nd	CHCl ₃	Traore et al., 2000
<i>N. latifolia</i>	L	EtOH (d)	Akpanabiatu et al., 2005b
<i>N. latifolia</i>	SB	MeOH	Otimenyin and Uguru, 2007
<i>N. latifolia</i>	SB	MeOH : H ₂ O (80 : 80) (m)	Liu et al., 2011
<i>N. latifolia</i>	S	Aq (m)	Arise et al., 2012
<i>N. latifolia</i>	L	MeOH (m)	Akinloye and Olaniyi, 2012
<i>N. latifolia</i>	SB	Aq (m)	Kouadio et al., 2014
<i>N. latifolia</i>	L	EtOH : H ₂ O (70 : 30) (d)	Solomon et al., 2014a; 2014b
<i>N. latifolia</i>	L	Aq (d)	Magili et al., 2014
<i>N. latifolia</i>	RB, L	MeOH (d)	Oise et al., 2014
<i>N. latifolia</i>	SB, RB, L, F	EtOH : H ₂ O (70 : 30) (m)	Ogenyi et al., 2015
<i>N. pobeguinii</i>	SB	MeOH : H ₂ O (80 : 20) (m)	Mesia et al., 2005; 2010
<i>N. pobeguunii</i>	SB	MeOH : H ₂ O (80 : 80) (m)	Liu et al., 2011

Bark (B), Stem Bark (SB), Root (R), Root Bark (RB), Stem (S), Leaf (L), Fruit (F), Aq (Aqueous), m (maceration), d (decoction).

7. Conclusion

The genus *Nauclea* has been used in sub-Saharan Africa since decades in traditional medicine, and is still a center of interest for researchers and local populations, as witnessed by the number of articles — more than fifty — published in the last two years on the topic. The *Nauclea* genus has become even more popular since our recent reports regarding the occurrence of the analgesic tramadol in the roots of *Nauclea latifolia*. Thus, the consequent amount of bibliographical data clearly needs a compilation and critical analysis because publications are often poorly indexed in databases, their accesses are frequently difficult and numerous papers

are not written in English. African *Nauclea* species are still indicated today in sub-Saharan countries for a very wide range of pathologies among which infections, digestive ailments, pain and metabolic diseases are the most frequently cited, and including regionally specific illnesses such as malaria. *N. latifolia*, and in a lesser extent *N. diderrichii* and *N. pobeguinii*, have been heavily reported and constitute major remedies in some areas. However, very little is known to date about the traditional use of *N. nyasica*, *N. gilletii*, *N. vandergutchii* and *N. xanthoxylon* in relation to the low abundance of these species. Many of pharmacological evaluations of *Nauclea* extracts were conducted on different targets clearly overlapping local indications. An important part of these studies are of insufficient quality as they revealed a lack of internal control, standardization and literature comparison as well as low number of samples. Beside these weaknesses and the reports of some divergent results, the analysis of the pharmacological evaluation literature tends to validate traditional uses, as many extracts displayed biological effects initially suggested by local medicinal practices. However, the aqueous macerate, the major preparation mode for oral intake, was not always identified as the more efficient extracting mode.

Phytochemistry of the genus *Nauclea* has been extensively described and various classes of compounds are reported in several species. Among these, indoloquinolizidines appeared to be characteristic of this genus. However, while some activities of *Nauclea* extracts have been related to the presence of particular compounds, especially alkaloids — *e.g.* strictosamide —, some others are still away from any molecular rationalization of the observed effects. Furthermore, some concerns are persisting about the toxicity of *Nauclea* extracts that could be a source of adverse effects among populations using these traditional ingredients. It is worth noting that traditional utilization of *Nauclea* species should be structured in the future for maintaining sustainability of these plants, as *N. diderrichii* is already threatened. A special caution should be observed for certain rare species or for preparations using bark or roots which

are more destructive for the trees. In addition, the less studied *Nauclea* species (i.e. *N. xanthoxylon* and *N. nyasica*) clearly deserve further ethnopharmacological evaluations about their geographical distribution, traditional uses, pharmacological activities and chemical composition.

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