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

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ABSTRACT

Ethnopharmacoalogical relevance: The genus *Nauclea* in Africa comprises seven species. Among them, *N. latifolia*, *N. diderrichii* and *N. pobeguinii* are widely used by the local population in traditional remedies. Preparation from 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*. Concerning the chemical composition of the *Nauclea* genus, indoloquinolizidines alkaloids could be considered as the major class of compounds as they are reported in every analyzed *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 modes of traditional remedies.

1. Introduction

For centuries, medicinal plants of tropical sub-Saharan Africa have been extensively used by local communities for 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 a higher number of traditional healers — 1 for 500 patients (WHO, 2013) — as compared to that of physicians — 1 for 6700 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 the 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 this long-standing culture 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 Naucleeae with 17 genera

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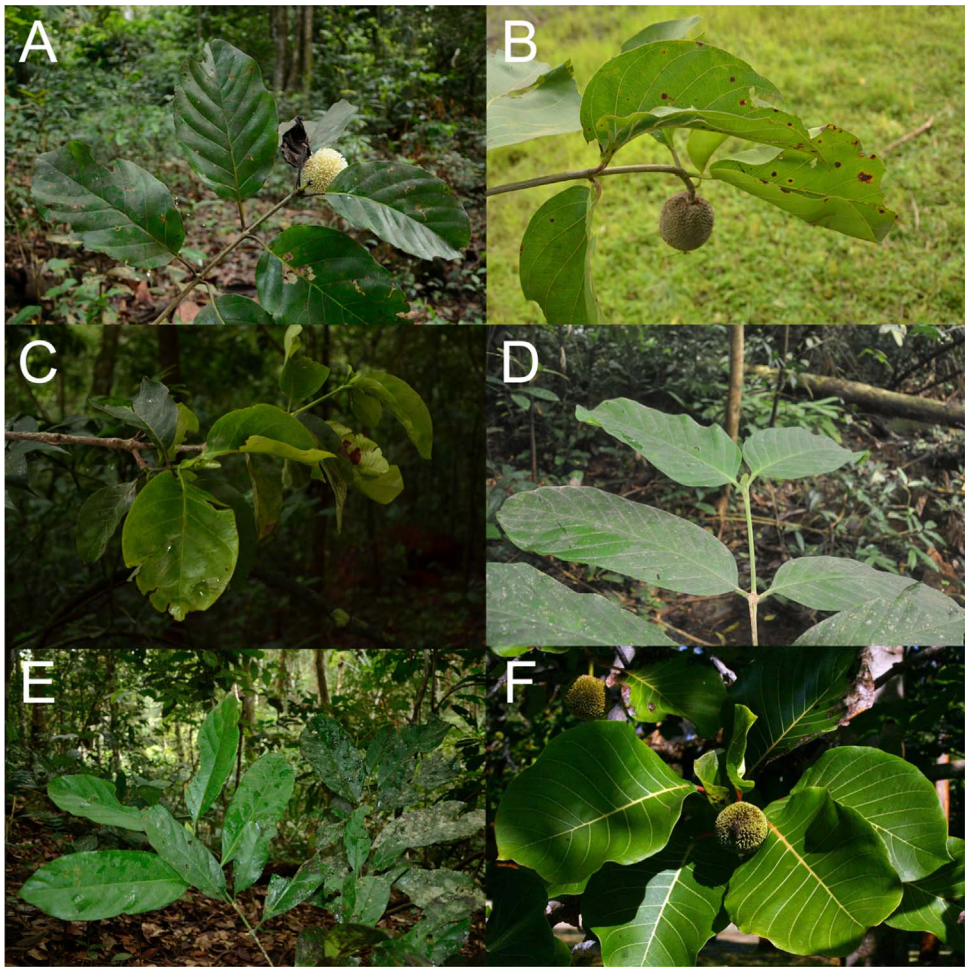

Fig. 1. Photographs of six African *Nauclea* species. A. *N. pobeguinii* (Gabon, credit: Ehoarn Bidault). B. *N. latifolia* (Guinea, credit: Ehoarn Bidault). C. *N. diderrichii* (Guinea, credit: Ehoarn Bidault). D. *N. vanderguchtii* (unknown location, credit: David Kenfa). E. *N. gilletii* (Gabon, credit: Ehoarn Bidault). F. *N. nyasica* (Zimbabwe, credit: Mark Hyde). The pictures are under Creative Commons licences (CC-BY-NC-ND or CC-BY-NC).

(Löfstrand et al., 2014). This group can be easily distinguished from those of other tribes 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 (Fig. 1). These trees have flattened terminal buds, and adpressed stipules deciduous or subpersistent, 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 (Fig. 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 (Fig. 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 remedies have been developed by local population to manage these illnesses. Besides, these ethnopharmacological data are widely supported by validated biological activities from both extracts and phytochemicals. The very recent clinical development of three antimalarial phytomedicinal preparations from *N. latifolia* (NIPRD-AM1; Gamaniel, 2009), *N. latifolia* in combination with *Cassia occidentalis* (Manalaria®; Pousset, 2006; Memvanga, 2015) and *N. pobeguinii* (PR 259 CT1; Mesia et al., 2011, 2012a, 2012b) in Nigeria for the first one and in the Democratic Republic of Congo for the two latter, 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.

1- Ovaries and fruitlets free ..... *Nauclea nyasica* (Hoyle) Å. Krüger & Löfstr.
[syn. *Burttdavya nyasica* Hoyle] Distribution: Tanzania to Mozambique

2- Ovaries and fruitlets persistently connate into a syncarp 3

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 pendulous 5

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 russeggeri* 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 headsacross corollas up to 40 mm, corolla lobes with 1–3 lines of hairs inside ..... *Nauclea gilletii* (De wild.) Merr.
[syn. *Sarcocephalus gilletii* De Wild., *Sarcocephalus trillesii* var. lancifolia A.Chev., *Nauclea lancifolia* (A.Chev.) Aubrév.] Distribution: Ivory Coast to WC. Trop. Africa.

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

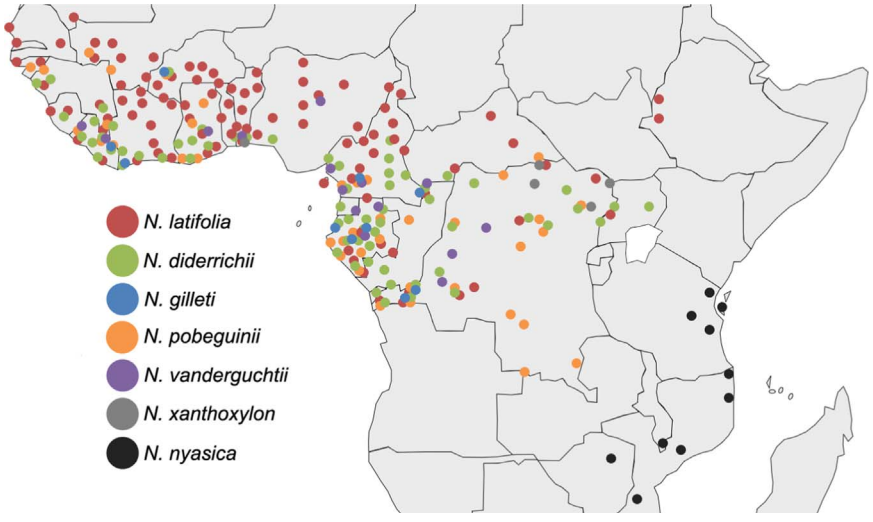

Fig. 3. General geographical distribution of the seven African *Nauclea* species. The dots are compiled observations of specimens from various occurrence datasets (e.g. Naturalis Biodiversity Center, Tropicos Specimen Data, Herbarium of the "Muséum National d'Histoire Naturelle" of Paris, West African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

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

Species	*Plant parts*	*Uses*	*References*
N. diderrichii	W	Timber for building	Towns (2014)
	B	Aphrodisiac	Towns (2014)
	B	Bitter agent in place of hob for local beer fabrication	Desobgo et al. (2013)
	Sd	Ground detoxification properties	Omorogie et al. (2012)
	S	Crafts and energy wood	Sibirina et al. (2014)
N. latifolia	S	Lumber and energy wood	Adeniyi (2015)
	F	Food for human, source of ascorbic acid	Ambé (2001), Ambé and Malaisse (2001)
N. pobeguinii	F	Food for gorillas	Breuer (2003)
N. vanderguchtii	S	Timber and furniture	Obute and Ekiye (2008)
N. xanthoxylon	W	Lumber and energy wood	Dossou et al. (2012)

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

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. No data were found concerning *N. nyasica* non-medical ethnobotanical uses.

Nauclea diderrichii wood is used as high-value primary material in building industries in West Africa, due to the high quality of its timber (strength and durability) and its resistance to termites (Towns, 2014). A survey conducted among 200 aboriginals showed the wide applications of *N. diderrichii* trunk for crafts, mortar for building housing, energy wood and canoe construction (Sibirina et al., 2014). The bark is also used as an aphrodisiac (Towns, 2014), 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 International Union for Conservation of Nature (IUCN) Red List of Threatened Species, with a “vulnerable” status (IUCN, 2016). The plant also displays a detoxifying property. Indeed, in a recent report it was described the ability of seeds to absorb the chromium (III) in aqueous solution (Omorogie et al., 2012). This property is of particular interest, as *N. diderrichii* 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, in Congo, a study conducted on mammals 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 properties of Nauclea spp

As mentioned above, the recent clinical assays undertaken on 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. pobeguinii* 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. pobeguinii*, 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%; Iyamah 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; Iyamah 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, 2010; Asase and Oppong-Mensah, 2009), 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 in water, various plant parts (leaves, roots, bark) are used, even within the same region. *Nauclea* species are highly cited by both traditional healers and herbal medicine sellers (Yetein et al., 2013). Conversely, when local populations (e.g. housewives, farmers) have been interviewed, the citation frequencies occasionally dropped (Asase et al., 2005; Dike et al., 2012). Finally, *Nauclea* species are used either alone or in recipes including other various plants.

3.1.2. Anti-helminthic properties of Nauclea spp

From Sierra Leone to Angola, extracts of *N. latifolia* are used as anti-helminthic agents (Göhre et al., 2016) (Table 3). The roots, bark, stem or leaves are prepared, often through water 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 water decoctions of *N. diderrichii* and *N. pobeguinii* have also been described as traditional anti-helminthic remedies in D.R. Congo (Mesia et al., 2005; Mbuta et al., 2012; Luzakibanza Manzo, 2012).

3.1.3. Antiviral properties of Nauclea spp

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 4). It as to be noticed that, as etiology of jaundice was not described in the cited publication, viral infections are not the only causes of icterus which could be treated by these extracts. *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 D.R. Congo (Mbuta et al., 2012) for treating jaundice and hepatitis respectively.

3.1.4. Antimicrobial properties of Nauclea spp

As a treatment for dysentery and diarrhea, *N. latifolia*, *N. diderrichii* and *N. pobeguinii* 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 5). 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, gonorrhea 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; Luzakibanza Manzo, 2012). Besides these indications, extracts of *Nauclea* species are

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

Species	Plant part (extraction mode)	Country	Region	% of citation	Administration mode (Dose)	References
N. diderrichii	B (d)	Benin	Plateau of Allada	52%[a]	Oral intake	Yetein et al. (2013)
N. diderrichii	nd	Cameroon	Dja Biosphere Reserve	nd	nd	Betti (2004)
N. diderrichii	B, R, F	Cameroon	Mount Cameroon	nd	nd	Ndenecho (2009)
N. diderrichii	nd	Ivory Coast	Tanoé-Ehy Forest	nd	nd	Zadou et al. (2011)
N. diderrichii	R, SB, F	Nigeria	nd	nd	nd	Chukwuma et al. (2015)
N. diderrichii	SB (d)	Nigeria	South Nigeria	9%[a]	nd	Iyamah and Idu (2015)
N. diderrichii	nd	nd	Congo basin forests	nd	nd	Eto (2013)
N. latifolia	R (d)	Benin	Plateau of Allada	86%[a]	Oral intake	Yetein et al. (2013)
N. latifolia	R, S	Burkina Faso	nd	nd	nd	Kristensen and Balslev (2003)
N. latifolia	R, L (d, m)	Burkina Faso	Baskoure, Kourittenga Province	12%[b]	nd	Nadembega et al. (2011)
N. latifolia	SB, R (d)	Cameroon	Yaoundé & Mbalmayo	nd	Oral intake (mixture with other, various species)	Tsabang et al. (2012)
N. latifolia	R (d)	D.R. Congo	All regions	19%[a]	nd	Luzakibanza Manzo (2012)
N. latifolia	S (m)	Ghana	Accra, Central, Eastern & Ashanti Regions	9%[a]	Oral intake	Asase and Oppong-Mensah (2009)
N. latifolia	R (m), L (d)	Ghana	Wechiau Community Hippopotamus Sanctuary area	5%[a]	Oral intake	Asase et al. (2005)
N. latifolia	R (d)	Ghana	Dangme West District	21%[a]	Oral intake (ad libitum)	Asase et al. (2010)
N. latifolia	RB (i)	Ghana	North West	nd	Oral intake	Asase and Oteng-Yeboah (2012)
N. latifolia	nd	Ghana	nd	nd	Mixture with other, various species	Osei-Djarbeng et al. (2015)
N. latifolia	L, SB, RB (d)	Guinea	All regions	12%[a]	nd	Traore et al. (2013)
N. latifolia	R	Guinea	Fuuta Jallon area	nd	nd	Kamsu-Foguem et al. (2013)
N. latifolia	SB (d)	Mali	nd	nd	nd	Ahua et al. (2007)
N. latifolia	L (d), B (m)	Mali	All regions	nd	Oral intake, optionally with *Balanites aegyptiaca* 2–3 times a day for 3 days to one week) and bath	Badiaga (2011)
N. latifolia	L (d, oral & bath)	Mali	Sélingué subdistrict	66%[a]	Oral intake and bath	Diarra et al. (2015)
N. latifolia	L (d), B, R	Mali	nd	nd	nd	Nordeng et al. (2013)
N. latifolia	SB, R, L (m)	Nigeria	Middle Belt, Southern region	nd	Mixture with other species	Adebayo and Krettli (2011)
N. latifolia	L	Nigeria	South-western	0.2%[a]	nd	Dike et al. (2012)
N. latifolia	L (d)	Nigeria	Ogbomoso, South West	nd	Oral intake (mixture with other species, 1 glass cup twice a day)	Olorunnisola et al. (2013)
N. latifolia	R, (m, d, i)	Nigeria	Akwa Ibom State	3%[b]	nd	Ajibesin et al. (2008)
N. latifolia	R, B, L (t, d)	Nigeria	Okeigbo, Ondo state, southwest	nd	nd	Odugbemi et al. (2007)
N. latifolia	R, S, L	Nigeria	All regions	nd	nd	Gbile and Adesina (1987)
N. latifolia	L, SB, R (t, d)	Nigeria	Southern	46%[a]	nd	Iyamah and Idu (2015)
N. latifolia	Combined plants	Nigeria	nd	nd	nd	Abd El-Ghani (2016)
N. latifolia	L	Nigeria	Okigwe Imo State	nd	Mixture with other species	Uzodimma (2013)
N. latifolia	L (i)	Nigeria	Ekiti state	nd	Oral intake	Olorunniyi and Morenikeji (2013)
N. latifolia	B, R (d)	Nigeria	Ogun state	8%[b]	Mixture with other, various species	Adeyemi et al. (2010)
N. latifolia	L	Nigeria	Ogun state	nd	Oral intake	Adekunle (2008)
N. latifolia	B	Nigeria	SW	nd	nd	Omobuwajo et al. (2008)
N. latifolia	nd	Senegal	nd	nd		Kerharo and Adam (1974)
N. latifolia	nd	Sierra Leone	Bo	50%[a]	Alone or in mixture with other, various species	Ranasinghe et al. (2015)
N. latifolia	L	Sierra Leone	nd	nd	Oral intake (once per day)	Kanteh and Norman (2015)
N. latifolia	L (d), R (d)	Sierra-Leone	Kpaa Mende	nd	Oral intake and bath (mixture with other various species)	Lebbie and Guries (1995)
N. latifolia	R (d, m)	Togo	Maritime region	nd	Oral intake	Koudouvo et al. (2011)
N. latifolia	AP (d)	Togo	nd	nd	nd	Tittikpina et al. (2016)
N. latifolia	R (m), L	Togo	nd	50%[b]	Oral intake (mixture with other various species)	Tchacondo et al. (2011)
N. latifolia	nd	Togo	Plateau region	48%[a]	Oral intake	Agbodeka et al. (2016)
N. pobeguinii	SB (d)	D.R. Congo	District of Sankuru	nd	nd	Mesia et al. (2005)
N. pobeguinii	SB (d, m)	D.R. Congo	All regions	17%[a]	nd	Luzakibanza Manzo (2012)
N. pobeguinii	SB (m)	Guinea	All regions	7%[a]	nd	Traore et al. (2013)

(*continued on next page*)

Table 2 (*continued*)

Species	Plant part (extraction mode)	Country	Region	% of citation	Administration mode (Dose)	References
N. pobeguinii	L (d)	Mali	Sélingué subdistrict	55%[a]	Oral intake and bath	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), (if not stated otherwise, all extractions were made in water), Democratic Republic of Congo (D.R. Congo).

[a] specific study on this indication.

[b] including other indications.

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.

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).

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; Luzakibanza 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 (Ndenecho, 2009). *N. latifolia* leaves are also used for the later indication (Badiaga, 2011; Lekana-Douki et al., 2011).

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 lead 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).

3.5. Respiratory diseases

Fumigations of *N. latifolia* seeds are prescribed in D.R. Congo

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

Species	Plant part (extraction mode)	Country	Region	% of citation	Administration mode (Dose)	References
N. diderrichii	SB (d)	D.R. Congo	Equateur Province	nd	Enema (half a glass twice daily), oral intake	Mbuta et al. (2012)
N. latifolia	R, B (directly consumed, m, d)	Angola	Uige	Most cited plant[a]	Enema or oral intake	Göhre et al. (2016)
N. latifolia	R (d)	Congo	Brazzaville	11%[a]	nd	Ahombo et al. (2012)
N. latifolia		Ghana	Ashanti region	2%	nd	Agyare et al. (2014)
N. latifolia	S, L	Nigeria	Nasarawa state	3%	nd	Ibrahim et al. (2016)
N. latifolia	L (d)	Sierra Leone		nd	Application on the belly	Kanteh and Norman (2015)
N. latifolia	R, L (d)	Sierra-Leone	Kpaa Mende	nd	Oral intake (with *Cassia sieberiana*)	Lebbie and Guries (1995)
N. latifolia	AP (d)	Togo		nd	nd	Tittikpina et al. (2016)
N. pobeguinii	SB (d)	D.R. Congo	District of Sankuru	nd	nd	Mesia et al. (2005)
N. pobeguinii	SB (d, m)	D.R. Congo	All regions	nd	nd	Luzakibanza Manzo (2012)

Aerial parts (AP), Stem Bark (SB), Root (R), Stem (S), Leaves (L), decoction (d), maceration (m), (if not stated otherwise, all extractions were made in water), Democratic Republic of Congo (D.R. Congo).
[a] including other indications.

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.

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; Gidado 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 anti-hypertensive 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).

3.7. Reproduction and sexual dysfunctions

The three most ethnopharmacologically relevant species *N. latifolia*, *N. diderrichii* and *N. pobeguinii* are indicated for treating sexual and reproductive dysfunctions (Table 11). Stem bark of *N. pobeguinii* in D.R. Congo (Mesia et al., 2005; Luzakibanza Manzo, 2012) and bark of *N. diderrichii* in Cameroon and Gabon (Nole et al., 2016; Towns, 2014) are reported for managing sexual asthenia. Infusions of *N. latifolia* roots are 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 consumed for the same indication (Betti et al., 2013). Female infertility is 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 enhancing the reproductivity (Diame, 2010) and the use of roots 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, 2014). 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).

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 leaves or root extracts of *N. latifolia* (Shomkegh et al., 2016; Aniama et al., 2016). This latter extract is also indicated for dermatosis (Erinoso et al., 2016) whereas leaves and bark of *N. vanderguchtii* (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).

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), for its anticancer properties (Ashidi et al., 2010) or more generally for good health (Kristensen and Balslev, 2003). Finally, *N. xanthoxylon* root, leaf and bark are used in traditional medicine in Angovè forest (Benin) without any mention of indications (Dossou et al., 2012).

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

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

Traditional use	Species	Plant part (extraction mode)	Country	Region	% of citation	Administration mode (Dose)	References
Jaundice	*N. diderrichii*	W (d)	Gabon	Ipassa Biosphere Reserve	1%	Oral intake, enema	Betti et al. (2013)
	N. latifolia	L, R (i)	Nigeria	All regions	nd	nd	Gbile and Adesina (1987)
	N. latifolia	R (d)	Nigeria	Ogun state	nd	Oral intake (1 cup daily)	Erinoso and Aworinde (2012)
	N. latifolia	R	Nigeria	Abeokuta	nd	Oral intake (1 small cup daily)	Idu et al. (2010)
	N. latifolia	Inner B, S, sap, R, F, RB	Nigeria	Lagos state	nd	nd	Olowokudejo et al. (2008)
Yellow fever	*N. latifolia*	R	Nigeria	Enugu state	nd	Oral intake (1 glass thrice daily)	Aiyeloja and Bello (2006)
	N. latifolia	(d)	Nigeria	Ogun state	11%[a]	Several recipes with other plants	Adeyemi et al. (2010)
	N. latifolia	R (m)	Nigeria	Benue state	nd	nd	Shomkegh et al. (2016)
	N. latifolia	L (d)	Sierra-Leone	Kpaa Mende	nd	Bath (in combination with other plants)	Lebbie and Guries (1995)
Hepatitis	*N. diderrichii*	B (d)	D.R. Congo	Equateur Province	nd	Oral intake (1 glass twice daily during 7 days)	Mbuta et al. (2012)
AIDS	*N. latifolia*	R, RB	Uganda	Sembabule, Kamuli, Kabale and Gulu districts	20%[b]	nd	Lamorde et al. (2010)
Measles	*N. latifolia*	Inner B, S, sap, R, F, RB	Nigeria	Lagos state	nd	nd	Olowokudejo et al. (2008)
Flu and measles	*N. latifolia*	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), (if not stated otherwise, all extractions were made in water), Democratic Republic of Congo (D.R. Congo).
[a] including other indications, [b]specific study on this indication., nd: no data.

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 (Fig. 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* (Kuete et al., 2015). The general steroid precursor squalene has also been found in *N. latifolia* (Ngnokam et al., 2003).

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* (Figs. 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. pobeguinii*. Naucledine, desoxycordifolinic acid (*N. diderrichii*; MacLean and Murray, 1970; Murray et al., 1972; Adeoye and Waigh, 1983b), strictosidine, desoxycordifoline (*N. pobeguinii*; Xu et al., 2012) and 3α,5α-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 naucledine) or diderroside (for the four other compounds) derivatives (Fig. 6).

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 derived from nauclefine contains no less than fourteen different structures (Fig. 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. pobeguinii* (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: naucletine (*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. pobeguinii*; 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. pobeguinii* (Zeches et al., 1985), and several derivatives are also *Nauclea* constituents: 3,14-dihydroangustoline, 19-*O*-methyl-3,14-dihydroangustoline (*N. pobeguinii*; Xu et al., 2012), and latifoliamides D and E (*N. latifolia*; Agomuoh et al., 2013).

Alternatively, strictosamide-based indolo[2,3-a]quinolizidines can

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

Traditional use	Species	Plant part (extraction mode)	Country	Region	% of citation	Administration mode (Dose)	Reference
General antimicrobial use	*N. latifolia*	SB (m)	Guinea	All regions	0.2%	Oral intake	Magassouba et al. (2007)
	N. latifolia	L (d), F (m), B (d), R (m)	Mali	All regions	nd	nd	Badiaga (2011)
	N. latifolia	R (m)	Uganda	Bulamogi	nd	Oral intake (m in beer made from Musa × paradisiaca L. var. sapientum)	Tabuti et al. (2003)
	N. latifolia	nd	Nigeria	SW	nd	nd	Lawal et al. (2010)
	N. latifolia	R, L	Burkina Faso	Malon village	nd	nd	Sourabié et al. (2013)
	N. pobeguinii	SB (m)	Guinea	All regions	0.5%	Oral intake	Magassouba et al. (2007)
Scalp infection	*N. latifolia*	R (d)	Nigeria	Ibadan	nd	Oral intake or bath (in combination with other plants)	Aworinde and Erinoso (2015)
Abcsess	*N. latifolia*	R (d)	Nigeria	Ibadan	nd	Oral intake or bath (in combination with other plants)	Aworinde and Erinoso (2015)
Gale	*N. diderrichii*	nd	Ivory Coast	Tanoé-Ehy Forest	nd	nd	Zadou et al. (2011)
	N. latifolia	L	Sierra-Leone	Kpaa Mende	nd	nd	Lebbie and Guries (1995)
Thrush	*N. latifolia*	Inner B, S, sap, R, F, RB	Nigeria	Lagos state	nd	nd	Olowokudejo et al. (2008)
Lepra	*N. latifolia*	R, L	Burkina Faso	Baskoure, Kourittenga Province	3%[a]	nd	Nadembega et al. (2011)
Sexually transmitted infections	*N. latifolia*	B	Nigeria	Ibadan	2%	nd	Gbadamosi and Egunyomi (2014)
	N. latifolia	R, SB (d)	Nigeria	Okigwe Imo state	nd	Boiled with potash	Uzodimma (2013)
Gonorrhea	*N. diderrichii*	R, SB, F	Nigeria	nd	nd	nd	Chukwuma et al. (2015)
	N. latifolia	R (d)	Congo	Brazzaville	11%[a]	nd	Ahombo et al. (2012)
	N. latifolia	R (d)	Nigeria	Rivers state	FL = 65[b]	Oral intake (1 glass thrice daily)	Ajibesin et al. (2012a)
	N. pobeguinii	R	Nigeria	Adamawa State	nd	nd	Mac Donald and Olorunfemi (2000)
	N. pobeguinii	SB (d)	D.R. Congo	District of Sankuru	nd	nd	Mesia et al. (2005)
	N. pobeguinii	SB (d, m)	D.R. Congo	All regions	nd	nd	Luzakibanza Manzo (2012)
Typhoid	*N. diderrichii*	B, R, F	Cameroon	Mount Cameroon	nd	nd	Ndenecho (2009)
	N. latifolia	B, R (d)	Nigeria	Ogun state	8%	Mixture with other, various species	Adeyemi et al. (2010)
	N. latifolia	R (d)	Angola	Uige	Most cited plant[a]	Oral intake	Göhre et al. (2016)
Dysentery / Diarrhea	*N. diderrichii*	nd	Ivory Coast	Tanoé-Ehy Forest	nd	nd	Zadou et al. (2011)
	N. diderrichii	R, SB, F	Nigeria	nd	nd	nd	Chukwuma et al. (2015)
	N. diderrichii	SB (m)	Gabon	Ipassa Biosphere Reserve	1%	nd	Betti et al. (2013)
	N. diderrichii	R (d)	Ghana	Brong Ahafo	nd	Oral intake	Sam et al. (2013)
	N. latifolia	L	Ivory coast	Abidjan	1%	nd	Ambe et al. (2015)
	N. latifolia	L	Sierra Leone	nd	nd	bath	Kanteh and Norman (2015)
	N. latifolia	R, RB	Uganda	Sembabule, Kamuli, Kabale and Gulu districts	5%[a]	nd	Lamorde et al. (2010)
	N. latifolia	R (d)	Congo	Brazzaville	5%	nd	Ahombo et al. (2012)
	N. latifolia	B	The Gambia	nd	nd	nd	Madge (1998)
	N. latifolia	F	Sierra-Leone	Kpaa Mende	nd	nd	Oliver-Bever (1983)
	N. pobeguinii	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), (if not stated otherwise, all extractions were made in water), Democratic Republic of Congo (D.R. Congo), nd : no data.

[a] including other indications.

[b] : Fidelity Level: FL (%) = Np/N × 100 (Np 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).

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

Traditional use	Species	Plant part (extraction mode)	Country	Region	% of citation	Administration mode (Dose)	References
Dental and oral care	*N. diderrichii*	B, R, F	Cameroon	Mount Cameroon	nd	nd	Ndenecho (2009)
	N. latifolia	S	Nigeria	Ekiti state	nd	Chewing stick	Kayode and Omotoyinbo (2008)
Digestive ailments	*N. latifolia*		Nigeria	Kaduna state	nd	nd	Mathias et al. (2013)
Facilitate Digestion	*N. latifolia*	F (eating)	Cameroon	Sudano-sahelian	low	nd	Jiofack et al. (2010)
	N. diderrichii	B (d)	Nigeria	Niger delta	nd	Enema	Ubom (2010)
	N. diderrichii			Congo basin forests	nd	nd	Eto (2013)
Emetic	*N. latifolia*	Inner B, S, sap, R, F, RB	Nigeria	Lagos state	nd	nd	Olowokudejo et al. (2008)
Stomach problems	*N. diderrichii*	B, R, S		Central Africa	nd	nd	Eyong (2007)
	N. diderrichii	B, R, F	Cameroon	Mount Cameroon	nd	nd	Ndenecho (2009)
	N. latifolia	F, B, R	Cameroon	Mbembe Forest Reserve	nd	nd	Sainge et al. (2014)
	N. latifolia	Inner B, S, sap, R, F, RB	Nigeria	Lagos state	nd	nd	Olowokudejo et al. (2008)
	N. latifolia		Ghana	Northern	nd	Oral intake or bath	Insoll (2011)
	N. latifolia	L (i)	Burkina Faso	Western	nd	nd	Taïta (2003)
	N. latifolia	R (powder)	Togo	Tem tribe	32%	Oral intake	Tchacondo et al. (2011)
Constipation	*N. diderrichii*			Congo basin forests	nd	nd	Eto (2013)
	N. latifolia	L, R (d)	Sierra-Leone	Kpaa Mende	nd	Oral intake	Lebbie and Guries (1995)
Purgative	*N. diderrichii*	SB	Cameroon	Yaoundé markets	0.8%	nd	Betti (2002)
Hernia	*N. latifolia*	R, L	Burkina Faso		3%[a]	nd	Nadembega et al. (2011)
	N. latifolia	R, F (m)	Uganda	Bulamogi	nd	nd	Tabuti et al. (2003)
Haemorrhoids	*N. latifolia*	L (d)	Togo	Tem tribe	26%[a]	Oral intake or emena	Tchacondo et al. (2011)
	N. latifolia	R, B (d)	Burkina Faso	Western	nd	nd	Taïta (2003)
	N. latifolia	R	Congo	Kinshasa city	6%	Oral intake (2 glasses daily)	Ngbolua et al. (2016)

Bark (B), Stem Bark (SB), Root (R), Root Bark (RB), Stem (S), Leaves (L), Fruit (F), decoction (d), maceration (m), (if not stated otherwise, all extractions were made in water), nd: no data.
[a] including other indications.

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 (Fig. 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 3α,5α-tetrahydrodeoxycordifoline lactam (*N. pobeguinii* and *N. diderrichii*; Lamidi et al., 2005; Xu et al., 2012). Several 16,17-dihydro derivatives were discovered, such as naucleofficine D (*N. pobeguinii*; 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. pobeguinii*; 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. pobeguinii*; Xu et al., 2012).

Besides the two aforementioned subfamilies of indolo[2,3-a]quinolizidines, eight additional analogues with various structures have been described to date (Fig. 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. pobeguinii*; Mao et al., 1984; Anam, 1997).

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 (Fig. 10). Four pyrane-based compounds have been reported so far from African species of genus: cadambine (*N. latifolia*; Hotellier et al., 1979), 3α-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).

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

Finally, tramadol, a synthetic alkaloid known as strong analgesic, has been extracted by Boumendjel et al. from *N. latifolia* in 2013 (Fig. 12). Following this discovery, a controversy emerged about the origin of the presence of tramadol in the plant roots, i.e. natural vs. anthropologic. 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).

4.3. Phenolic compounds

Six phenol derivatives have been isolated from the three main species of African *Nauclea* (Fig. 13): antiarol (*N. diderrichii*; MacLean

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

Traditional use	Species	Plant part (extraction mode)	Country	Region	% of citation	Administration mode (Dose)	References
Toothache	*N. diderrichii*	B, R, F	Cameroon	Mount Cameroon	nd	nd	Ndenecho (2009)
Headache	*N. diderrichii*	B, R, F	Cameroon	Mount Cameroon	nd	nd	Ndenecho (2009)
	N. latifolia	L (d)	Mali	All regions	nd	Bath or oral intake (1 glass thrice or 4 times daily)	Badiaga (2011)
	N. latifolia	nd	Gabon	Haut-Ogooué Province	nd	nd	Lekana-Douki et al. (2011)
Abdominal- / stomach-ache	*N. latifolia*	B	Nigeria	Bauchi State	nd	nd	Adamu et al. (2005)
	N. latifolia	nd	Gabon	Haut-Ogooué Province	nd	nd	Lekana-Douki et al. (2011)
	N. latifolia	R, L	Burkina Faso	Baskoure, Kourittenga Province	3%[a]	nd	Nadembega et al. (2011)
	N. latifolia	B (d, m), R (d, m)	Mali	All regions	nd	Oral intake (1 glass twice or thrice daily) or emena	Badiaga (2011)
	N. latifolia	R (d)	D.R. Congo	All regions	19%[a]	nd	Luzakibanza Manzo (2012)
	N. latifolia	L, R (i)	Senegal	Kédougou	2%[a]	nd	Gning et al. (2014)
	N. latifolia	R (m, d)	Angola	Uige	Most cited plant[a]	Oral intake or emena	Göhre et al. (2016)
	N. latifolia	R	Gambia	nd	nd	nd	Madge (1998)
	N. latifolia	R, F, L	Burkina Faso	nd	0.7%	nd	Kristensen and Balslev (2003)
	N. pobeguinii	SB (d)	D.R. Congo	District of Sankuru	nd	nd	Mesia et al. (2005)
Backache	*N. latifolia*	R, F (i)	Uganda	Bulamogi	nd	nd	Tabuti et al. (2003)
	N. latifolia	R	D.R. Congo	Kinshasa city	medium	nd	Ngbolua et al. (2016)
Lumbago	*N. latifolia*	R (d), L (d)	Nigeria	Kainji Lake National Park	nd	Oral intake or bath	Amusa et al. (2010)
	N. diderrichii	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), (if not stated otherwise, all extractions were made in water), Democratic Republic of Congo (D.R. Congo), nd: no data.
[a] including other indications.

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).

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; Ettebong 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 several improved traditional medicines in D.R. Congo and Nigeria using *N. pobeguinii* and *N. latifolia.* A combination of *N. latifolia* and *Cassia occidentalis,* named Manalaria®, was approved by D.R. Congo governement and included in the Congolese List of Essential Drugs (Pousset, 2006; Memvanga, 2015; LNME, 2010).

Two improved traditional medicines are currently under development in Nigeria. The 80% ethanol extract of *N. pobeguinii* was evaluated in vivo in mice (*P. berghei* and *P. yoeli* N67 mouse models) at the orally dose of 300 mg/kg and led to the decrease of malaria symptoms on both models (86% on *P. berghei* and 75% *P. yoeli* N67) (Pieters, 2008; Mesia et al., 2005). Moreover, levels of creatinine, urea, aspartate-aminotransferase and alanine-aminotransferase were unmodified after treatment and no acute toxicity was observed in mice after a dose of 2 g/kg (Mesia et al., 2010). Consequently, this extract was investigated under phase 1 of clinical trials for the treatment of uncomplicated malaria under the name PR 259 CT1. The herbal composition was formulated in a gelatin capsule with 500 mg of PR 259 CT1 and administered three times per days (each 8 h for 7 days) to 15 healthy volunteers according to the process described for malaria patients (Mesia et al., 2011). This clinical study revealed only mild side effects and underscored the significant safety and tolerability of PR 259 CT1 in healthy volunteers. The phase IIA assessed the efficiency on uncomplicated parasitic infection as ten patients over eleven were completely cleared of parasitic symptoms and fever (Mesia et al., 2012a). The phase IIB was conducted as a single blind prospective trial by using a mixture of artesunate-amodiaquine (AS + AQ, Coaresucam®, the standard first-line treatment for uncomplicated malaria) as positive control. A rapid decrease of malaria symptoms was observed in both groups (Mesia et al., 2012b). The aqueous root extract of *N. latifolia*, called NIPRD AM1®, was studied in a comparative randomized clinical trial in uncomplicated malaria. Results showed a superior efficiency of NIPRD AM1® compared to controls chloroquine or sulphadoxine/pyrimethamine combination and without serious side effects (Gamaniel, 2009). Phytochemical and physicochemical experiments (Ameh et al., 2010, 2013) as well as standardization of the extract (Ameh et al., 2014) and metabolism studies (Adzu et al., 2013) were conducted to further develop NIPRD AM1®. Despite several studies on their safety and efficiency, these two last improved traditional medicines are still under development.

Overall, the alkaloid strictosamide is likely to be a main contributor to the antimalarial activities of *N. latifolia* and *N. pobeguinii* extracts, as the compound was found in various parts of these two taxa, sometimes at very high concentrations. Indeed, the amount of strictosamide in the PR 259 CT1 extract was determined to 5.6% (Mesia et al., 2011), and assays on chloroquine-resistant and chloroquine-sensitive strains of *P. falciparum* showed that the isolated molecule induced promising inhibition in both cases, with IC_{50} values of 0.90 and 0.74 μM respectively

Table 8
Uses of African Nauclea species against fever.

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

Bark (B), Root (R), Root Bark (RB), Stem (S), Leaves (L), Fruit (F), decoction (d), (if not stated otherwise, all extractions were made in water), nd: no data.

(Abreu and Pereira, 2001b). However these results were tempered by other authors (Del Rayo Camacho et al., 2004; He et al., 2005). Besides, five other alkaloids exhibited moderate activities in vitro, i.e. tetrahydrodesoxycordifoline, naucleidinal (from *N. latifolia*), 19-*O*-methylangustoline (from *N. pobeguinii*) and angustoline (from *N. latifolia* and *N. pobeguinii*), but these compounds usually occur at low concentrations in the reported extracts (Sun et al., 2008; Mesia et al., 2010).

The antihelmintic efficacy of *N. latifolia* was studied with various approaches and several models (Table 14). In sheep, with acute or subacute 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 of body weight compared to untreated control (Ademola et al., 2006) or with an efficiency at 1600 mg/kg comparable to the group treated with the antiparasitic drug, albendazole (5 mg/kg) (Onyeyili et al., 2001). The larvicidal activity of hot, cold water and ethanolic extracts on *Heligmosomodes bakeri* larvae at 5000 µg/mL was assessed. The mortality rate of L_1 larvae was 77%, 89% and 74% for hot, cold water and ethanolic extracts respectively while for L_2 larvae, 83%, 78% and 83% mortality rates were observed (Wabo Poné et al., 2012). Furthermore, aqueous extracts of *N. latifolia* leaves paralyzed *T. columbriformis* L_3 larvae with an EC_{50} 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 IC_{50} of 15 and 28 mg/mL respectively (Fakae et al., 2000).

Several compounds from *Nauclea* species were identified as GST inhibitors, i.e. strictosamide, naucleamide A and naucleamide F, with IC_{50} values between 20 and 30 µM (Ata et al., 2009).

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% compared to 88% for *N. latifolia* extract).

If no *N. diderrichii* extracts with anti-leishmanial properties have been reported to date, nine quinovic acid derivatives from the plant, together with the alkaloid cadambine acid, were tested both on promastigote and amastigote forms. In each case, the inhibition levels were low against intracellular amastigotes ($IC_{50} > 250$ µM), but far more interesting against promastigotes, with IC_{50} values between 1 and 3 µM, except for two compounds which showed less potential (Di Giorgio et al., 2006).

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 on the 6th day after treatment at a dose range of 40–100 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 anti-amoebic activity with minimum amoebicidal concentrations ≤ 5 µg/mL (Tona et al., 2000, 2009).

5.1.2. Antimicrobial

The antimicrobial activity of *N. latifolia* has 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 and fungi strains were tested (Table 15). The available data present few conclusions due to conflicting results by different authors. However, the key following points emerged: *(1)* an overall good anti-bacterial activity of alcoholic extracts of all parts of the plant against a broad spectrum of pathogens including Gram-negative and 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 remains very difficult and further complicated by the lack of standardization in antimicrobial evaluations and the absence of a common reference as positive control. Nonetheless, *N.*

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

Traditional use	Species	Plant part (extraction mode)	Country	Region	% of citation	Administration mode (Dose)	References
General use	*N. latifolia*	Seeds	D.R. Congo	All regions	nd	Fumigation (twice daily)	Disengomoka et al. (1983)
	N. latifolia	B	Angola	Uige	Most cited plant[a]	Directly consumed	Göhre et al. (2016)
Cough	*N. diderrichii*	B, R, F	Cameroon	Mount Cameroon	nd	nd	Ndenecho (2009)
	N. latifolia	Inner B, S, sap, R, F, RB	Nigeria	Lagos state	nd	nd	Olowokudejo et al. (2008)
	N. latifolia	Inner B	Sierra-Leone	Kpaa Mende	nd	nd	Lebbie and Guries (1995)
Asthma	*N. latifolia*	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), maceration (m), (if not stated otherwise, all extractions were made in water), Democratic Republic of Congo (D.R. Congo), nd: no data.

[a] including other indications.

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

Traditional use	Species	Plant part (extraction mode)	Country	Region	% of citation	Administration mode (Dose)	References
Anti-diabetic	*N. diderrichii*	nd	Benin	nd	1%	nd	Laleye et al. (2015)
	N. diderrichii	B (d)	Cameroon	Coastal rain forest	nd	Oral intake (2 glasses thrice daily)	Nole et al. (2016)
	N. latifolia	R	Benin	Cotonou, Abomey-Calavi	0.5%	nd	Fah et al. (2013)
	N. latifolia	R (d)	Congo	nd	nd	nd	Muziazia et al. (2015)
	N. latifolia	R	Congo	Kinshasa city	medium	Oral intake (2 glasses daily)	Ngbolua et al. (2016)
	N. latifolia	SB (d)	Ivory Cost	Agboville	nd	Oral intake	N'Guessan et al. (2009)
	N. latifolia	SB (d)	Guinea	Coastal lowlands	nd	nd	Diallo et al. (2012)
	N. latifolia	L, F, R, B	Guinea	Conakry	3%[a]	nd	Baldé et al. (2006)
	N. pobeguinii	L, B	Guinea	Conakry	8%[a]	nd	Baldé et al. (2006)
Diuretic	*N. latifolia*	R, L	Burkina Faso	Baskoure	0.7%[b]	nd	Nadembega et al. (2011)
	N. latifolia	R (d)	Congo	Brazzaville	13%[b]	nd	Ahombo et al. (2012)
	N. diderrichii	B (d)	Cameroon	Coastal rain forest	nd	Oral intake (2 glasses thrice daily)	Nole et al. (2016)
	N. diderrichii	B, R, F	Cameroon	Mount Cameroon	nd	nd	Ndenecho (2009)
Anti-hypertensive	*N. latifolia*	L, R, S	Nigeria	Edo State	2%	Oral intake (1/2 or 1 glass daily)	Gbolade (2012)
	N. latifolia	R	Nigeria	Ogbomoso	30%[c]	Oral intake (1 tablespoon daily)	Olorunnisola et al. (2015)
	N. latifolia	R (d)	Benin	Ouémé	3%	Oral intake	Lagnika et al. (2016)
Blood thinner	*N. diderrichii*	B, R, F	Cameroon	Mount Cameroon	nd	nd	Ndenecho (2009)
Anaemia	*N. diderrichii*	B (d)	Benin	Plateau of Allada	34%[b]	nd	Yetein et al. (2013)
Appetite suppressant	*N. latifolia*	F	Burkina faso	nd	3%	Raw fruits consumption	Pare et al. (2016)

Bark (B), Stem Bark (SB), Root (R), Stem (S), Leaves (L), Fruit (F), decoction (d), (if not stated otherwise, all extractions were made in water), nd: no data.
[a] percentage of users.
[b] including other indications.
[c] specific study on cardiovascular diseases.

pobeguinii root, bark and leaf methanolic extracts were evaluated as antimicrobials and were found as inhibitors of bacterial growth on several pathogen strains (Njimoh et al., 2015; Seukep et al., 2016). Moreover a synergistic effect toward various usual antibiotics was shown, thereby validating their use during treatment of resistant bacteria strains.

It is generally difficult to link these activities with the phytochemical components of the *Nauclea* genus. If strictosamide was evaluated on a large spectrum of Gram-positive and Gram-negative bacteria species, it revealed only a modest action in all cases (Li et al., 2012; Ezem et al., 2015). Similar low activities were recorded for strictosamide, as well as for *N. latifolia* constituents naucleamides A and F, against fungi (Ezem et al., 2015; Ata et al., 2009).

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 LC_{50} 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 (IC_{50} = 5.4 µg/mL) and aciclovir resistant (IC_{50} = 7.8 µg/mL) strains on the HSV-2 model chosen.

The *Nauclea* major constituent strictosamide was found as an antiviral with moderate potency, especially against influenza A (IC_{50} = 649 µg/mL on strain A/PR8/34(H1N1) and 26 µg/mL on strain A/Jinan/15/90) and B (IC_{50} = 323 µg/mL on strain B/Jingfang/76/98) viruses and respiratory syncytial virus (IC_{50} = 12.5 µg/mL; Li et al., 2012, 2015).

5.2. Digestive

Digestive activities of *N. latifolia* were reported through antidiarrheal and anti-ulcer evaluations (Table 17). The hydro-alcoholic extract from the root bark 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 an 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). The effects of aqueous and methanolic leaf extracts on gastric acid secretion were also investigated and a significant and dose-dependent decrease was observed. The total gastric acid content was lowered at 9.8 µEq HCl/100 g of body weight and 6.1 at a dose of 400 mg/kg for methanol and water extracts respectively (control: cimetidine 5.6 µEq HCl/100 g of body weight at 100 mg/kg) (Balogun et al., 2014, 2015). The hydro-alcoholic extract did not exhibit any protective effect on aspirin-induced ulcer in rats (Orole et al., 2013). The anti-ulcer activity of a stem bark hydro-methanolic extract was also investigated in histamine and aspirin-induced ulcer models in rats. This extract significantly increased ulcer tolerance rate compared to controls at 50 mg/kg but was found ineffective at 100 mg/kg (Alaribe et al., 2014). The same material was found potent on *Helicobacter pylori* with MIC of 25 mg/mL (amoxicillin: MIC = 3.1 mg/mL) (Alaribe et al., 2014).

5.3. Pain and other neurological disorders uses

Many studies have been conducted on neurological 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

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

Traditional use	Species	Plant part (extraction mode)	Country	Region	% of citation	Administration mode (Dose)	References
Sexual asthenia	*N. diderrichii*	B (d)	Cameroon	Coastal rain forest	nd	Oral intake (2 glasses thrice daily)	Nole et al. (2016)
	N. diderrichii	B, W	Gabon	Mont Bouët and Ngouema	nd	nd	Towns (2014)
	N. pobeguinii	SB (d, m)	D.R. Congo	nd	nd	nd	Mesia et al. (2005)
	N. pobeguinii	SB (d, m)	D.R. Congo	All regions	nd	nd	Luzakibanza Manzo (2012)
Premature ejaculation	*N. latifolia*	R (i)	Uganda	Bulamogi	nd	nd	Tabuti et al. (2003)
Male sexual dysfunction	*N. diderrichii*	L (t)	Gabon	Ipassa Biosphere Reserve	nd	Oral intake	Betti et al. (2013)
	N. latifolia	RB (alcohol)	Ethiopia and Nigeria	Ethiope West and Delta state of Nigeria	nd	Oral intake (4–5 tablespoons twice daily)	Fasola et al. (2014)
	N. latifolia	R (directly consumed or d)	Angola	Uige	Most cited plant[a]	Oral or enema	Göhre et al. (2016)
	N. latifolia	R (d)	Mali	Bandiagara	nd	Oral intake (3 glasses thrice daily)	Badiaga (2011)
Female infertility	*N. diderrichii*	SB	Cameroon	Yaoundé markets	0.6%	nd	Betti (2002)
	N. latifolia	R, L	Burkina Faso	nd	0.7%[a]	nd	Nadembega et al. (2011)
	N. latifolia	L, R (d)	Congo	Brazzaville	12%[b]	Oral intake in combination with other plants (1/2 glass daily)	Nkounkou-Loumpangou et al. (2005)
	N. latifolia	R, B (tincture), R (i in alcohol)	Nigeria	Lagos state	nd	nd	Makinde et al. (2015)
	N. latifolia	R (d)	Togo	nd	Most cited plant[a]	nd	Tchacondo et al. (2011)
Menstrual disorder	*N. latifolia*	Inner B, S, sap, R, F, RB	Nigeria	Lagos state	nd	nd	Olowokudejo et al. (2008)
	N. latifolia	B	Nigeria	Southwestern	nd	nd	Omobuwajo et al. (2008)
	N. latifolia	R	Benin and Gabon	nd	Most cited plant[b]	nd	Towns and Van Andel (2014)
Reproductive health	*N. latifolia*	B	Ghana	Western	0.1%	nd	Diame (2010)
Women's health	*N. latifolia*	R (dry)	Benin	nd	nd	bath	Quiroz (2015)
Uterine fibroids	*N. latifolia*	R	Uganda	Bulamogi	nd	nd	Tabuti et al. (2003)
Anti-abortifacient	*N. pobeguinii*	B	Cameroon	Upper Nyong valley forest	nd	nd	Jiofack et al. (2009)
	N. pobeguinii	B	Cameroon	All regions	nd	nd	Njamen et al. (2013)
Effective abortifacient	*N. latifolia*	R	Ghana	nd	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), (if not stated otherwise, all extractions were made in water), Democratic Republic of Congo (D.R. Congo), nd: no data.

[a] including other indications.

[b] specific study on this indication.

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

Traditional use	Species	Plant part (extraction mode)	Country	Region	% of citation	Administration mode (Dose)	References
Skin disease	*N. diderrichii*	B, R, F	Cameroon	Mount Cameroon	nd	nd	Ndenecho (2009)
	N. diderrichii	L	Nigeria	Keffi	29%[a]	nd	Mustapha et al. (2013)
	N. latifolia	S	Nigeria	Ekiti state	FL = 88[b]	nd	Kayode et al. (2015)
	N. latifolia	R (d)	Nigeria	Rivers state	FL = 65[b]	Oral intake (1 glass thrice daily for 5 days)	Ajibesin (2012b)
Itching	*N. latifolia*	R (d)	Nigeria	Benue state	nd	Bath (twice daily for 2 days)	Shomkegh et al. (2016)
Itching & filariasis	*N. latifolia*	L, R	Nigeria	Kogi state	nd	nd	Aniama et al. (2016)
Infantile dermatosis	*N. latifolia*	R (d)	Nigeria	Odeda	3%[a]	Oral intake in combination with other plants (2–3 teaspoons thrice daily)	Erinoso et al. (2016)
Dermatosis / wound	*N. vanderguchtii*	L, B	Cameroon	Sudano-sahelian	medium	nd	Jiofack et al. (2010)
Wound	*N. latifolia*	Inner B, S, sap, R, F, RB	Nigeria	Lagos state	nd	nd	Olowokudejo et al. (2008)
	N. latifolia	R, S	Sierra-Leone	Kpaa Mende	nd	nd	Lebbie and Guries (1995)
	N. latifolia	R	Gambia		nd	nd	Madge (1998)
Burn	*N. latifolia*	L (i)	Senegal	Kédougou	FL = 50[b]	Bath	Gning et al. (2014)

Bark (B), Root (R), Root Bark (RB), Stem (S), Leaves (L), Fruit (F), decoction (d), infusion (i), (if not stated otherwise, all extractions were made in water), nd: no data.
[a] specific study on dermatologic indication.
[b] Fidelity Level: FL (%) = Np/N × 100 (Np 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).

extracts of aerial parts. Aqueous and hydro-alcoholic extracts at 800 mg/kg lowered the number of writhing movements to 32 and 28 respectively. Administration of paracetamol at 50 mg/kg results in 20 movements while untreated group presented 65 movements. The reaction time on hot plate was delayed to 27 s by both extracts at 800 mg/kg (untreated: 5.2 s; morphine, 2 mg/kg: 57 s). An aqueous macerate of root bark at 200 mg/kg presented an inhibition of constriction of 95% similar to aspirin (Abbah et al., 2010). The same publication also described a dose-dependent activity of this extract using hot plate model. Evaluations on acetic acid-induced writhing model were conducted with methanolic extract of stem bark (Otimenyin and Uguru, 2007) and also demonstrated a weak analgesic effect. Total alkaloids extracts of root and leaf (10 mg/kg) were found moderately active on the same model with an important sample variability from a potentialisation of 5.9–23.5% of inhibition for roots and 8.2–26% of inhibition for leaves (Badiaga, 2011). Besides, studies on other neurologic properties of *N. latifolia* were conducted by Taïwe and colleagues. They first assessed anticonvulsant, anxiolytic and sedative effects on mice of aqueous root extract using open field and elevated plus maze test (Ngo Bum et al., 2009). During the hole-board evaluation on mice, a comparable anxiolytic effect of the same type of extract at 160 mg/kg to diazepam at 0.5 mg/kg was observed (Taïwe et al., 2010). The same authors also reported a myorelaxant effect using horizontal wire test where *N. latifolia extract* (160 mg/kg) presented similar activity as the control (diazepam: 1 mg/kg) (Taïwe et al., 2010). The force swimmed test was used to evaluate antidepressant effect. The swimming time of mice treated with an aqueous root extract at 160 mg/kg was found to be similar to the control group (fluoxetine: 10 mg/kg) (Taïwe et al., 2010). An assessment of the analgesic effect was also performed through acetic acid-induced writhing, formalin-induced pain, hot-plate and tail immersion evaluations. During the writhing test, a dose of 160 mg/kg led to an inhibition 62%, higher than aspirin at 150 mg/kg (54%) but lower than morphine at 5 mg/kg (20%). Globally, all the analgesic assays performed on this extract were consistent with this performance scale: lower activity than morphine but higher than aspirin (Taïwe et al., 2011). Finally, a bioactive-guided fractionation allowed the identification of an alkaloid-containing fraction as the one which mostly carried the analgesic effect (Taïwe et al., 2014). Studying an ethanolic extract of fruits in comportemental experiments on a rat model, Shamoun et al. (2014) demonstrated sedative and anxiolytic properties since 200 mg/kg. An anticonvulsant effect was also reported through several induced seizures tests at doses higher than 400 mg/kg (Shamoun et al., 2014). However, the same type of extract did not show any significant anxiolytic activity during behavioral evaluation on mice model at doses of 200, 400 and 600 mg/kg (Arome et al., 2014). A reduction of the exploratory behavior, spontaneous motor activity and a prolongation of pentobarbital-induced sleeping time on mice after feeding with an aqueous macerate (50 mg/kg) have also been mentioned (Amos et al., 2005). At 100 mg/kg, the exploratory behavior decreased in a similar way as if using nitrazepam (2 mg/kg). Furthermore, methanolic leaf and root extracts of *N. latifolia* were evaluated and found able to potentialize purinergic neurotransmission using a rat bladder model (Udoh, 1995).

The active principle from an analgesic fraction of *N. latifolia* was recently identified as the known drug tramadol, reported for the first time as a natural product in 2013 (Boumendjel et al., 2013). Marketed in 1977, tramadol exhibits about 10% of the potency of morphine and has been widely used as an analgesic for moderate to severe acute pain. Its presence in the roots of *N. latifolia*, which could be associated with the traditional indications of the plant as painkiller, seemed to be very sensible to seasonality and sample location, as the analysis of other extracts of the same type not always yielded the compound, or in various amounts (Kusari et al., 2014). This hypothesis was backed-up by another study that used an induced writhing movement test on mice: heterogeneous results were obtained from samples harvested in various locations with different climatic characteristics (Badiaga, 2011). As the

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

Traditional use	Species	Plant part (extraction mode)	Country	Region	% of citation	Administration mode (Dose)	References
	Ophthalmic						
Improve sight	*N. latifolia*	Sap	Sierra-Leone	nd	nd	Ocular (drop sap in the affected eye	Kanteh and Norman (2015)
Eye troubles	*N. latifolia*	Sap	Sierra-Leone	Kpaa Mende	nd	nd	Lebbie and Guries (1995)
Conjunctivitis	*N. latifolia*	L (d)	Ivory Coast	Abidjan	3%[a]	Ocular	Adiko et al. (2014)
	Infant illness						
Swollen spots on the head	*N. latifolia*	L (m)	Ethiopia	Mandura Woreda	nd	Oral intake (1 glass)	Mengesha (2016)
Thin children	*N. latifolia*	F	Gambia	nd	nd	nd	Madge (1998)
	N. latifolia	R	Burkina Faso	nd	0.1%	nd	Kristensen and Balslev (2003)
	Others indications						
For good health	*N. latifolia*	R, L	Burkina Faso	nd	0.1%	nd	Kristensen and Balslev (2003)
Rheumatism	*N. latifolia*	R	Gambia	nd	nd	nd	Madge (1998)
Fractured bones	*Nauclea* sp.	L	C.A.R.	nd	nd	nd	Thomas (1959)
SNC injuries	*N. latifolia*	L (d, bath)	Togo	All regions	19%[b]	nd	Kantati et al. (2016)
Anticancer	*N. latifolia*	R, L (d)	Nigeria	South-western	nd	Oral intake	Ashidi et al. (2010)
General use	*N. xanthoxylon*	B, L, R	Benin	Agonvè forest	medium	nd	Dossou et al. (2012)
	Veterinary uses						
Diarrhea	*N. latifolia*	R	Cameroon	nd	nd	nd	Souare et al. (2013)
	N. latifolia	L, SB, R	Nigeria	Plateau state	2%[a]	nd	Offiah et al. (2011)
Anti-helminthic	*N. latifolia*	L, SB (m)	Nigeria	Nasarawa state	nd	nd	Abu et al. (2009)
	N. latifolia	R (d)	Kenya	Ormaland	nd	nd	Swaleh (1999)
Horse fever	*N. latifolia*	R, B (d)	Cameroon	Gobo	nd	nd	Cardinale and Seignobos (2004)
Horse hernia	*N. latifolia*	R	Cameroon	Gobo	nd	nd	Cardinale and Seignobos (2004)

Bark (B), Stem Bark (SB), Root (R), Leaves (L), Fruit (F), decoction (d), maceration (m), (if not stated otherwise, all extractions were made in water), Central African Republic (C.A.R.), nd: no data.
[a] specific study on this indication.
[b] including other indications.

prominent constituent of most of the studied extracts, strictosamide was also evaluated for its analgesic action. The compounds did not induce any effect on the hot-plate tests, but it allowed an extended latent pain period in the writhing test at concentrations of 20–40 mg/kg (Li et al., 2014). Strictosamide also showed myorelaxant activity at 50–400 mg/kg with a concomitant decrease in motor activity and rectal temperature suggesting CNS depression (Candeias et al., 2009). If these activities could be related to monoamine oxidase A (MAO-A), butyrylcholinesterase (BChE) and acetylcholinesterase (AChE) inhibition, strictosamide was only a weak inhibitor of these enzymes, and thus probably acts through another pathway. However, angustine (from *N. latifolia* and *N. pobeguinii*) showed far more interesting activity on MAO-A (IC_{50} = 1.10 μM) and a selective BChE vs. AChE profile (IC_{50} = 3.47 μM vs. > 100 μM), and could be one of the active principles of some reported extracts (Passos et al., 2013a, 2013b). The analogue compound angustidine was even more active against BChE and AChE, while naucletine, nauclefine and angustoline were far less promising (Liew et al., 2015). In addition, two *N. latifolia* constituents, i.e. cadambine (from *N. latifolia*) and 3α-dihydrocadambine (from *N. latifolia* and *N. diderrichii*), displayed neuroprotective effects vs. glutamate-induced HT22 cell death (Qi et al., 2014), and 3α,5α-tetrahydrodesoxycordifoline (from *N. latifolia*, *N. pobeguinii* and *N. diderrichii*) reduced the effects of morphine withdrawal in guinea-pigs (Capasso et al., 1997). Finally, 3α,5α-tetrahydrodesoxycordifoline also inhibited electrically induced contractions of guinea-pig ileum (Aquino et al., 1996).

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 to induce hypertensive activity via adrenoreceptor stimulation (Udoh and Lot, 1998). Ethanolic root extract at 10 mg/kg also reduced the mean arterial pressure from 116 to 100 mm Hg and 157–72 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 reported elsewhere on rats treated with the ethanolic leaf extract (Akpanabiatu et al., 2005a).

Compounds from *N. latifolia* also showed weak antihypertensive properties. Latifoliamide C was found as a renin inhibitor (IC_{50} = 11.3 μM), however far less active than the reference aliskiren (IC_{50} = 0.0006 μM). Other latifoliamides were even less potent against this target (Agomuoh et al., 2013). Angustine, nauclefine and naucletine were also identified as potent vasodilators on an isolated rat aorta assay, with more than 90% relaxation at micromolar range (Liew et al., 2012). Naucledine from *N. diderrichii* also displayed moderate vasorelaxant effects in similar conditions (Mukhtar et al., 2012). Since these compounds are present in the plant in very small amounts, their

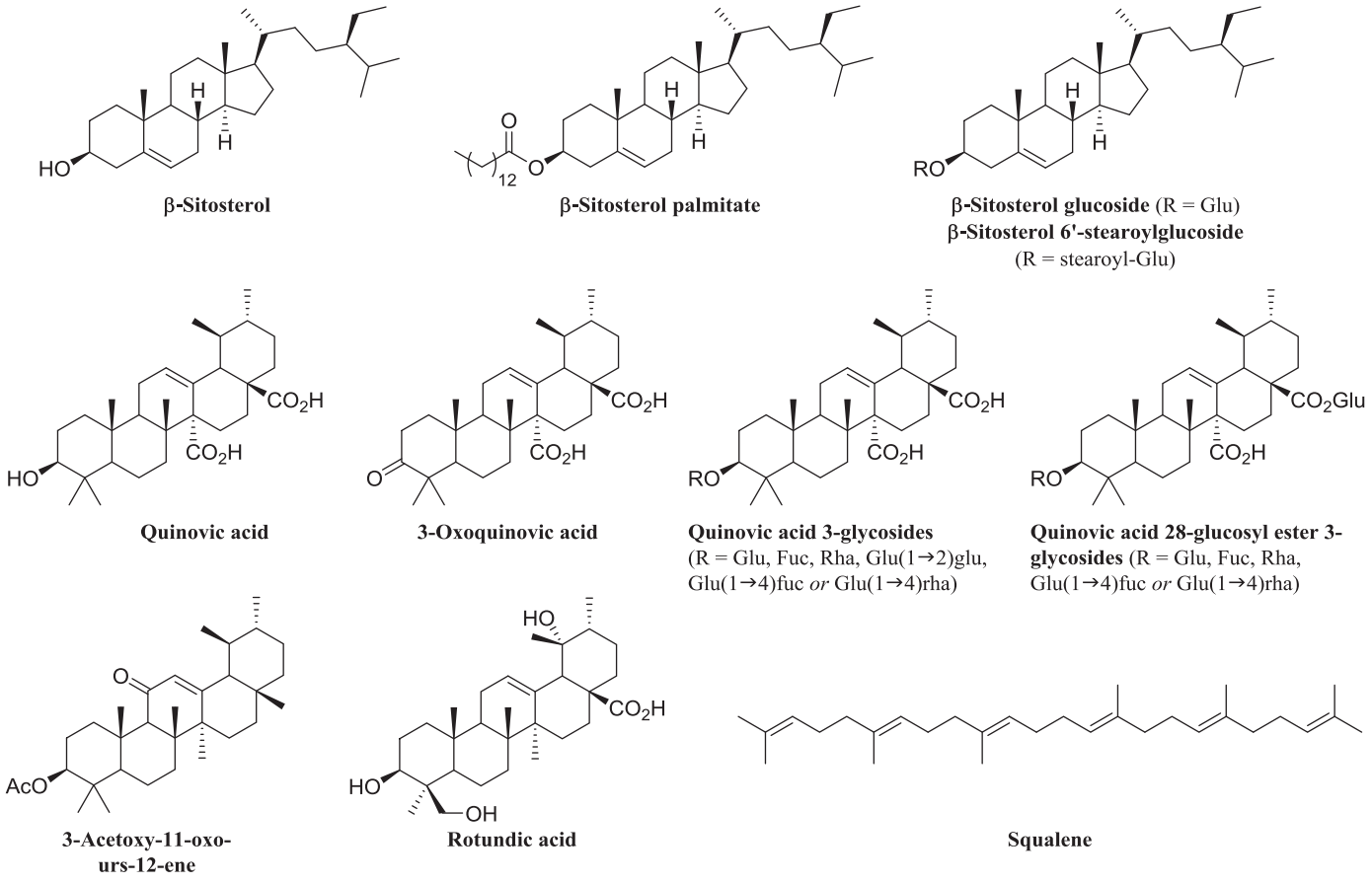

Fig. 4. Structure of steroids and saponins isolated from African *Nauclea* species.

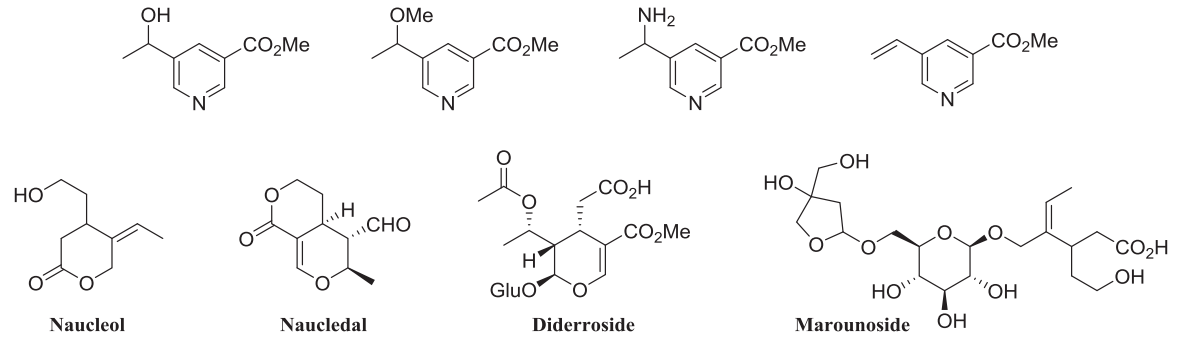

Fig. 5. Structure of nicotinate and terpenoid derivatives isolated from African *Nauclea* species.

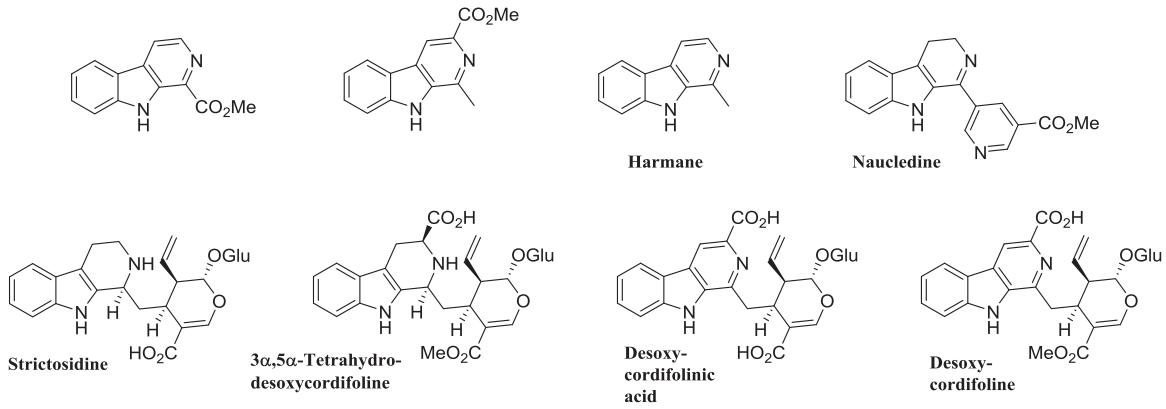

Fig. 6. Structure of simple β-carbolines isolated from African *Nauclea* species.

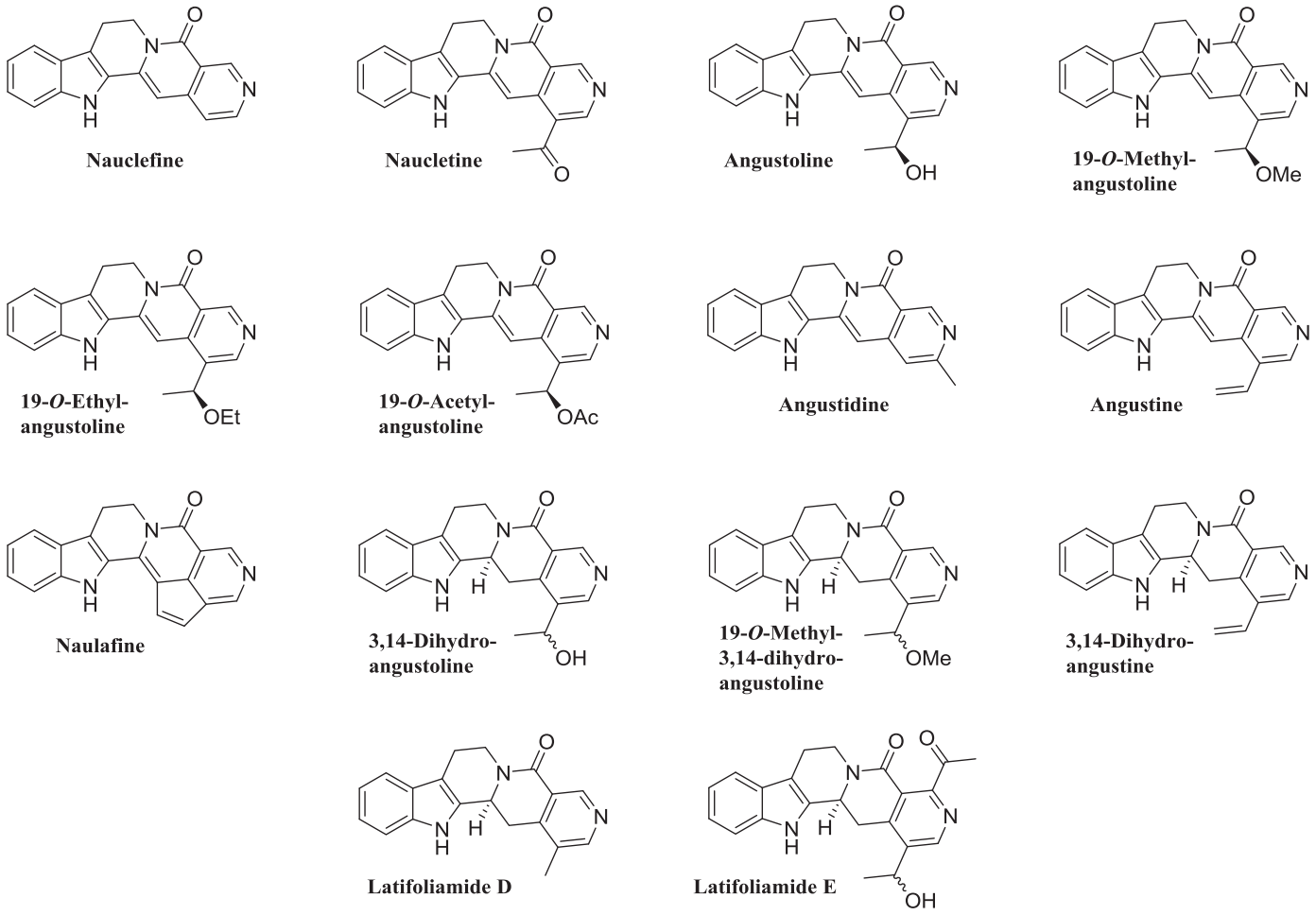

Fig. 7. Structure of nauclefine-based indolo[2,3-a]quinolizidine derivatives isolated from African *Nauclea* species.

contributions are unlikely to endorse the hypertensive activity of *Nauclea* extracts however.

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). An ethanolic leaf extract (200 mg/kg) was also evaluated on non-diabetic rats. Following oral and intraperitoneal glucose loads, the latter extract inhibited the increase of blood 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). Assessment of α-amylase inhibition by a methanolic stem bark extract of *N. diderrichii* revealed a potent inhibition effect with IC_{50} of 248 µg/mL, comparable to acarbose, the reference α-amylase inhibitor (IC_{50} = 177 µg/mL) (Ogbole et al., 2016). Similar results were obtained by Agnaniet *et al.* on aqueous extracts of bark and leaf (Agnaniet 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 (Agnaniet et al., 2016).

Otherwise, *N. latifolia* extracts administration led to changes in lipid metabolism. Hence, total cholesterol (TC) and high density lipoprotein (HDL) levels significantly decreased while low density lipoprotein (LDL) and triacylglycerol (TG) levels raised, all in a dose-dependent manner, after feeding normal rats with an aqueous stem extract (200–800 mg/kg) (Arise et al., 2012). Different results were obtained when ethanol leaf extract and its sub-fractions (100 mg/kg) 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 at 250 mg/kg to 20, 11, 16 mg/dL respectively (glibenclamide 5 mg/kg: 14 mg/dL) (Edet et al., 2011). Total cholesterol was lowered to non-hypertensive control values by both stem and root ethanolic extracts (150 and 300 mg/kg) 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 (170–51 mg/kg) did not present significant changes in the lipid profile of the experimental

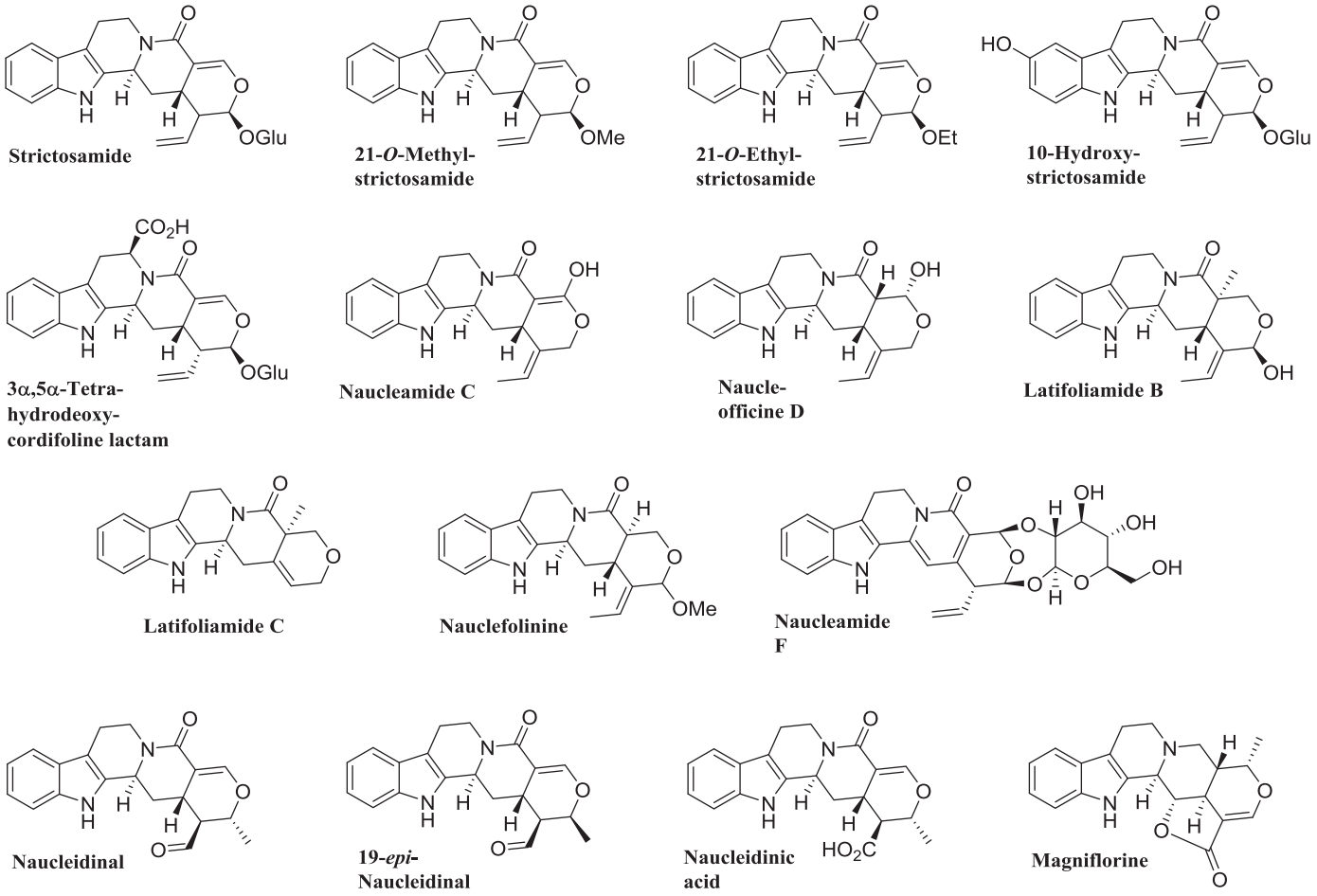

Fig. 8. Structure of strictosamide-based indolo[2,3-a]quinolizidine derivatives isolated from African *Nauclea* species.

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 ciprofloxacine showing a hypolipidaemic effect associated to an anti-lipid peroxidative efficiency at doses of 1200 or 2000 mg/kg (Chinedu et al., 2013). Cholesterolemia was measured on rats fed with crude fruits of *N. latifolia*. The supplementation by *N. latifolia* as total alimentation induced a dose-dependent hypocholesterolemic effect with a cholesterolemia of 85 mg/dL compared to control at 136 mg/dL (James and Ugbede, 2011).

The effects of *N. latifolia* roots extracts on hormones changes 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 (80 mg/kg) 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

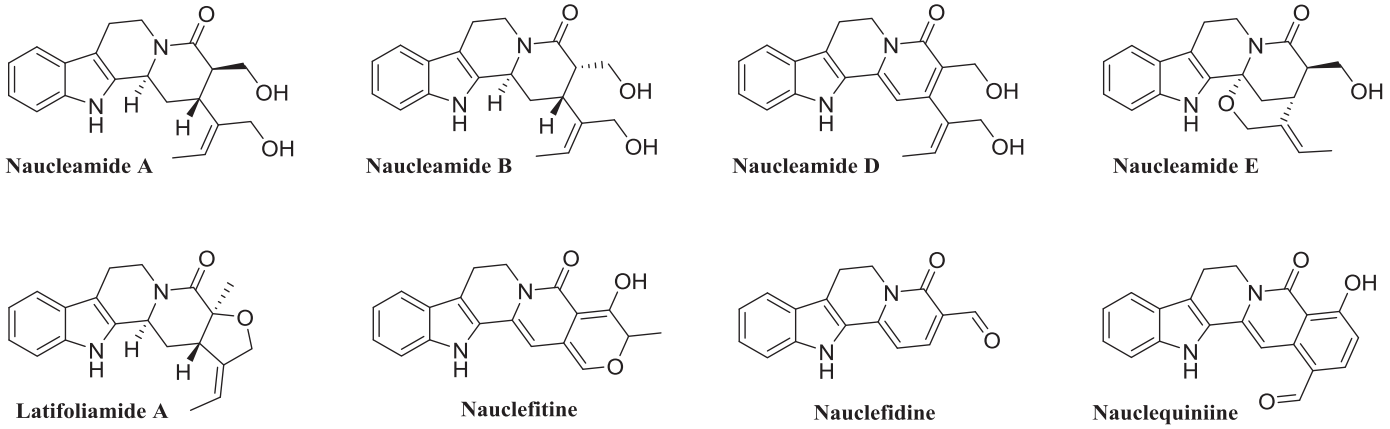

Fig. 9. Structure of other indolo[2,3-a]quinolizidine derivatives isolated from African *Nauclea* species.

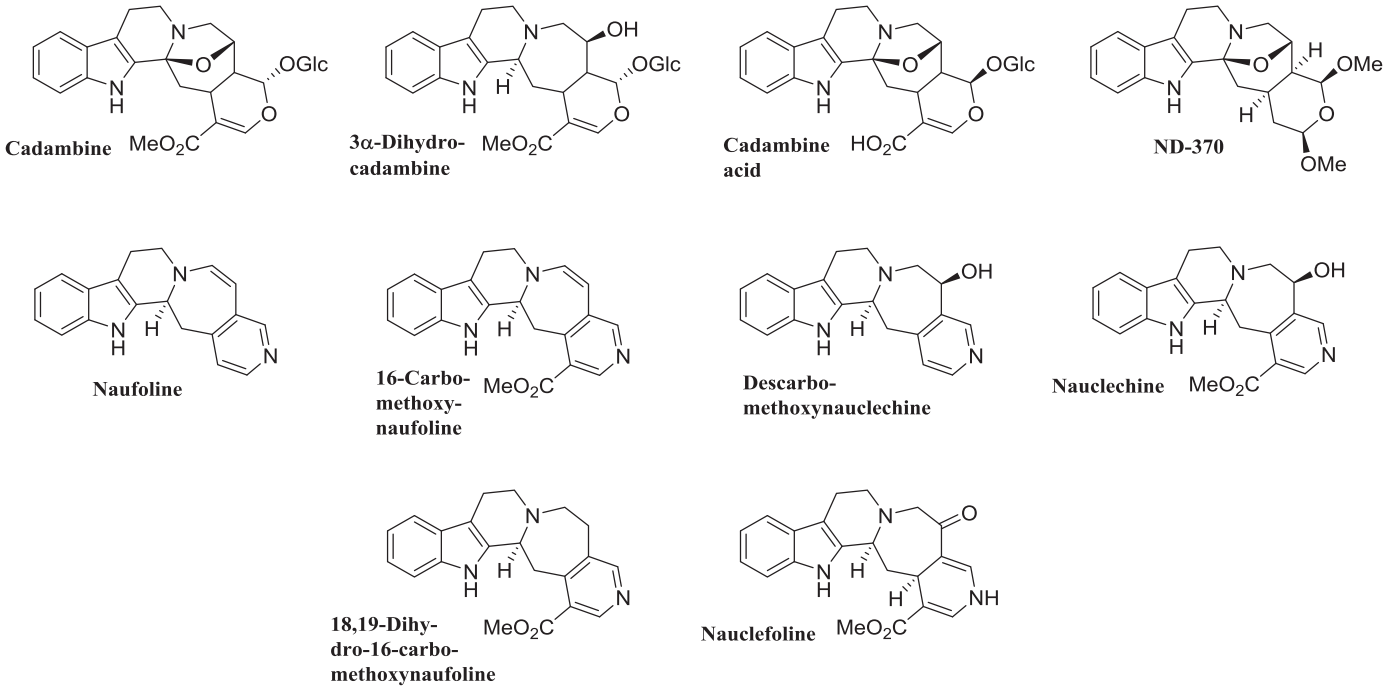

Fig. 10. Structure of indolo[2,3-a]pyrido[1,2-a]azepine derivatives isolated from African *Nauclea* species.

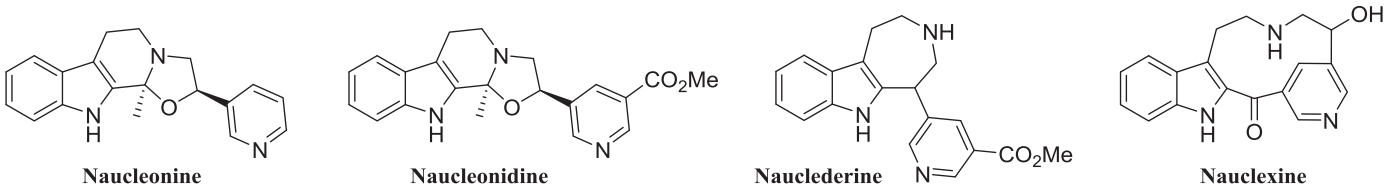

Fig. 11. Structure of other indole-based derivatives isolated from the genus *Nauclea*.

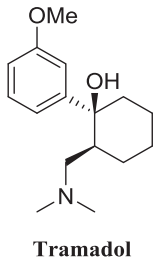

Fig. 12. Structure of tramadol, isolated from the roots of *N. latifolia*.

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).

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 edema on rodent. A reduction of edema was obtained since a dose of 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 a significant effect during 10 h (Amouzoun et al., 2008). Fever reduction due to administration of the aqueous root extracts (at 4 h, 80 mg/kg) was reported comparable to aspirin (300 mg/kg) (Taïwe et al., 2011).

Several compounds from *N. latifolia*, i.e. angustine, angustoline, latifoliamide B and latifoliamide D showed significant anti-inflammatory activities in a lipopolysaccharide-induced nitric oxide assay, with IC_{50} values between 1.34 and 3.40 μM. Naucleofficine D, from *N. pobeguinii*, was less active (Chen et al., 2016).

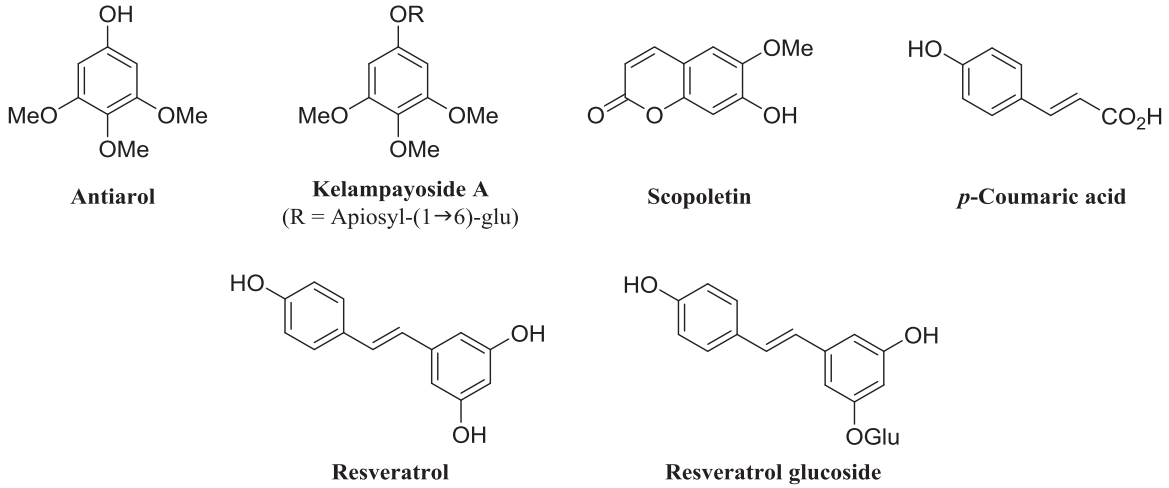

Fig. 13. Structure of phenolic compounds isolated from African *Nauclea* species.

Desoxycordifoline, a constituent of *N. diderrichii*, was identified as a weakly active in a glucocorticoid gene down-regulation assay, with 30% activity at 100 μM (Carroll et al., 2008). This plant has not provided anti-inflammatory extracts to date however.

5.6. Hepato-protective activity

Several studies were reported 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 CCl_4 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 an hepatoprotective effect on rats by *(1)* reducing the activity of γ-glutamyl transferase if raised by other factors (at 170 mg/kg) (Akpanabiatu et al., 2005b) *(2)* lowering AST, ALT levels and restoring normal proteinaemia in acetaminophen-treated rats (Effiong et al., 2013b, 2014).

5.7. Miscellaneous

Antioxidant activities on different parts of *N. latifolia* were described using various 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 an 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 IC_{50} 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

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

Properties	Species	*Plant parts*	*Extracts*	*References*
Anti-plasmodial	*N. latifolia*	S, R	Aq (m, d)	Benoit-Vical et al. (1998)
	N. latifolia	SB	EtOH (d)	Zirihi et al. (2005)
	N. latifolia	SB	MeOH (m)	Udobre et al. (2013a)
	N. latifolia	L	MeOH (m)	Udobre et al. (2013b)
	N. latifolia	L	Aq (d)	Dibua et al. (2013)
	N. latifolia	R	EtOH : H_2O (70 : 30) (m)	Adebajo et al. (2014)
	N. latifolia	L	EtOH : H_2O (70 : 30) (m)	Ettebong et al. (2014)
	N. latifolia	L	Aq (d)	Onyesom et al. (2015)
	N. pobeguinii	SB	MeOH : H_2O (80 : 20) (m)	Mesia et al. (2005, 2010, 2012a, 2012b)
	N. pobeguinii	SB	EtOH : H_2O (80 : 20)	Pieters (2008)
Anti-helminthic	*N. latifolia*	L	Aq	Asuzu and Njoku (1996)
	N. latifolia	L	MeOH : H_2O (50 : 50) (m)	Fakae et al. (2000)
	N. latifolia	L	Aq (d), EtOH (d)	Ademola et al. (2006)
	N. latifolia	SB	Aq (d)	Onyeyili et al. (2001)
	N. latifolia	SB	Aq (d and m), EtOH	Wabo Poné et al. (2012)
Anti-leishmanial	*N. latifolia*	SB	CH_2Cl_2 (m)	Ahua et al. (2007)
Trypanocidal	*N. latifolia*	RB	EtOH : H_2O (70 : 30) (d)	Madubunyi (1996)
No trypanocidal effect	*N. latifolia*	SB, L	MeOH (m)	Olanrewaju et al. (2014)
Anti-amoebic	*N. latifolia*	RB	*n*-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).

Table 15
Reported antimicrobial activities of African *Nauclea* species extracts[1].

Plant parts	*Extract*	*S. aureus*	*S. pneumoniae*	*B. cereus*	*S. dysentariae*	*B. subtilis*	*S. varidans*	*S. sonneri*	*E. coli*	*K. pneumonia*	*P. aeruginosa*	*S. parathypi*	*S.flexneri*	*S. typhi*	*Salmonella sp*	*A. niger*	*C. albicans*	*P. notatum*
N. latifolia																		
Stem Bark	Alkanes	–	–	+	+/–				–	–	–		–	–			–	
	$CHCl_3$	+			+	+	+		+	+	+					–	+/–	–
	EA	+		+	+	+			+/–	+	+		–	+		–	+	
	EtOH	+/–			+	+			+	+	–						+	
	MeOH	+	+	+	+	–	–		+/–	+/–	+	+	+	+		–	+/–	–
	Aq	+/–	–		+/–				+/–	+	–							
Unripe fruit	Alkanes	–				+			+	+	–			+				
	MeOH	–				–			+	+	+			+				
Ripe fruit	Alkanes	–				–			–	–	+			+				
	MeOH	+				+			–	+	+			+				
Leaf	Alkanes	+/–	–	+	+/–				–	–	+		+	+/–			+	
	$CHCl_3$	+							–		+			+/–				
	EA	+/–		+	+	+			+	+	+		+	+		+	+	
	EtOH	+			+				+/–	+	+/–			+/–				
	MeOH	+	+	+	+	+		–	+	+	+	+	+	+	–		+	
	Aq	+/–	+		+/–			–	+/–	+	+/–			+/–	+			
Root	$CHCl_3$	+					+		+		+			+/–				
	Et_2O	+									+			–				
	EtOH	+			+	+			+/–	+	+/–				+	+		
	MeOH	+					+		+/–		+/–			+				
	Aq	+/–			+	–	+		+/–	+	+/–			+/–				
N. pobeguinii																		
Bark	MeOH								+/–	–	–							
Leaf	MeOH								–	–	–							
Root	MeOH								+	+				+			+	

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

[1] 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), Fadipe et al. (2013), Ogueke et al. (2011), Okiei et al. (2011), Musa et al. (2011), Fagbohun et al. (2010), Okwori et al. (2008), Osadebe et al. (2010), Lagnika et al. (2011), Deeni and Hussain (1991), Okwori et al. (2008), Okechukwu et al. (2015), Okoli and Iroegbu (2004), Seukep et al. (2016), Njimoh et al. (2015).

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

Properties	*Species*	*Plant parts*	*Extracts*	*References*
Molluscicidal	*N. latifolia*	B	MeOH (m), Aq, (m)	Kela et al. (1989a), (1989b)
Anti-viral	*N. latifolia*	RB	MeOH : CH_2Cl_2 (50 : 50) (m)	Donalisio et al. (2013)

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

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

Properties	Species	*Plant parts*	*Extracts*	*References*
Anti-diarrheic	*N. latifolia*	RB	EtOH : H_2O (70 : 30) (m)	Owolabi et al. (2010)
Anti-ulcer	*N. latifolia*	L	Aq (i)	Balogun et al. (2013, 2014)
	N. latifolia	SB	MeOH : H_2O (50 : 50) (d)	Alaribe et al. (2014)
	N. latifolia	L	MeOH (d)	Balogun et al. (2015)
No anti-ulcer effect	*N. latifolia*	L	MeOH : H_2O (50 : 50) (m)	Orole et al. (2013)

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

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, meaning that the *N. latifolia* extract exhibits an antioxidant effect (Onyesom et al., 2015). These results were not confirmed by Edagha et al. (2015) who did not observe, using the same model, significant variations of antioxidant levels in the groups treated with ethanolic leaf extracts compared to control.

A constituent of *N. latifolia*, 3α,5α-tetrahydrodesoxycordifoline, was earlier identified as a scavenger of the DPPH radical, reaching an IC_{50} value of 47.1 μM (Cardoso et al., 2004). However, considering the small amounts (0.004% in the bark and wood) of this compound isolated from *N. latifolia* (Shigemori et al., 2003), its contribution could be neglectable. In the same study, the *N. diderrichii* component desoxycordifoline was found similarly active (IC_{50} = 49.9 μM), whereas no extracts from this plant have been reported as antioxidant to date (Cardoso et al., 2004).

The methanolic stem bark extract and its sub-fractions (100 mg/mL) were evaluated as cicatricing 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 IC_{50} values around 30 μg/mL on various cancer cell lines (Kuete et al., 2015).

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 (200–800 mg/kg) 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 of AST, ALT and creatinine. A high loss of water and depletion in sodium and potassium levels was observed in urine since (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 (250 mg/kg) was similarly evaluated and presented an increase of AST, ALT and AP levels in serum associated with histopathological lesions of liver and kidneys (Magili et al., 2014). Conducted on *Chinchilla* rabbit, a study targeting liver toxicity of an ethanolic crude extract of *N. latifolia* leaves, fruits, stem and root barks also demonstrated deleterious effects on hepatic functions. Elevation of AST and ALT activities was monitored for doses equal or above 250 mg/kg, and hepatic injuries were observed after 60 days of treatment at 150 mg/kg (Ogenyi et al., 2015). Liu et al. (2011) described genotoxic and clastogenic activity of a

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

Properties	Species	*Plant parts*	*Extracts*	*References*
Analgesic	*N. latifolia*	AP	EtOH : H_2O (m), Aq (m)	Okiemy-Andissa et al. (2004)
	N. latifolia	SB	MeOH	Otimenyin and Uguru (2007)
	N. latifolia	RB	Aq (m)	Abbah et al. (2010)
	N. latifolia	R, L, B	Alk	Badiaga (2011)
	N. latifolia	R	Aq (m)	Taïwe et al. (2011)
	N. latifolia	R	Acetone : H_2O (70 : 30) (m)	Taïwe et al. (2014)
Anticonvulsivant	*N. latifolia*	R	Aq (m)	Ngo Bum et al. (2009)
Anxiolytic and sedative	*N. latifolia*	RB	Aq (m)	Amos et al. (2005)
	N. latifolia	R	Aq (m)	Taïwe et al. (2010), Ngo Bum et al. (2009)
	N. latifolia	F	EtOH	Shamoun et al. (2014)
No anxiolitic effect	*N. latifolia*	F	EtOH (m)	Arome et al. (2014)
Myorelaxant	*N. latifolia*	R	Aq (m)	Taïwe et al. (2010)
	N. latifolia	F	EtOH	Shamoun et al. (2014)
Antidepressant	*N. latifolia*	R	Aq (m)	Taïwe et al. (2010)
Purinergic neurotransmission	*N. latifolia*	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).

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

Properties	*Species*	*Plant parts*	*Extracts*	*References*
Anti-hypertensive	*N. latifolia*	L	MeOH	Udoh and Lot (1998)
	N. latifolia	L, R	EtOH (d)	Akpanabiatu et al. (2005a)
	N. latifolia	R	EtOH (d), EtOH : H_2O (70 : 30) (d)	Nworgu et al. (2008), Nworgu et al. (2009)
	N. latifolia	RB, SB	EtOH : H_2O (80 : 20) (m)	Odey et al. (2012a)
Anti-diabetic	*N. latifolia*	L	Aq (m), EtOH (m)	Gidado et al., (2005, 2008)
	N. latifolia	L	Aq (d)	Iwueke and Nwodo (2008)
	N. latifolia	L	EtOH (m)	Gigado et al. (2009, 2012), Effiong et al. (2013a)
	N. latifolia	R, S	EtOH (m)	Yessoufou et al. (2013)
	N. latifolia	L	EtOH : H_2O (50 : 50) (m)	Antia and Okokon (2014)
	N. pobeguinii	B	Aq (d)	Agnaniet et al. (2016)
	N. diderrichii	L, B	Aq (m)	Agnaniet et al. (2016)
	N. diderrichii	SB	MeOH (m)	Ogbole et al. (2016)
Lipid metabolism	*N. latifolia*	L	EtOH (d)	Akpanabiatu et al. (2005a)
	N. latifolia	L	EtOH (m)	Edet et al. (2011)
	N. latifolia	F	MeOH (m)	James and Ugbede (2011)
	N. latifolia	S	Aq (m)	Arise et al. (2012)
	N. latifolia	RB, SB	EtOH : H_2O (80 : 20) (d)	Odey et al. (2012b)
	N. latifolia	L	MeOH	Chinedu et al. (2013)
	N. latifolia	R	Aq (d)	Effah (2014)
Hormonal activity	*N. latifolia*	R	Aq (i)	Rukundo (2007), Ishimwe (2008)
	N. latifolia	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).

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

Species	*Plant parts*	*Extracts*	*References*
N. latifolia	SB	MeOH	Otimenyin and Uguru (2007)
N. latifolia	L, R	MeOH : H_2O (50 : 50) (m)	Amouzoun et al. (2008)
N. latifolia	L, SB	MeOH	Osadebe et al. (2010)
N. latifolia	RB	Aq (m)	Abbah et al. (2010)
N. latifolia	R	Aq (m)	Taïwe et al. (2011)

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

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

Species	*Plant parts*	*Extracts*	*References*
N. pobeguinii	B, L	MeOH (m)	Kuete et al. (2015)
N. latifolia	RB	EtOH : H_2O (70 : 30) (d)	Madubunyi (1996)
N. latifolia	RB	MeOH	Udeh and Madubunyi (2008)
N. latifolia	RB	Aq (d)	Yesufu et al. (2010)
N. latifolia	L	EtOH (m)	Effiong et al. (2013b, 2014)
N. latifolia	L	MeOH (m)	Nwaehujor et al. (2016)
N. pobeguinii	L	Aq (d)	Kadiri et al. (2007)
N. latifolia	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).

hydro-methanolic bark extract of *N. latifolia*, *N. pobeguinii* and *N. diderrichii*, the later being the most toxic with a minimal active concentration of 23 µg/mL. The authors linked this activity to the various saponins found in these extracts. Mesia et al. (2005) did not observe toxic effect after acute or prolonged treatment of 4 weeks of *N. pobeguinii* stem bark extract on mice and described a $LD_{50} > 5$ g/kg. Moreover, no major lesions were found in the considered organs after a dose of 2 g/kg (Mesia et al., 2010). Evaluated on brine shrimp lethality assay, a methanolic macerate of stem bark of *N. diderrichii* showed a LC_{50} value of 1 µg/mL. Ethanolic leaf extract (500 mg/kg) administrated on gestational rat model induced 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 IC_{50} values around 30 µg/mL on various cancer cell lines (Kuete 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 LD_{50} 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 23).

Compounds from *Nauclea* were essentially studied through cytotoxicity assays. Especially, angustine, angustoline, nauclefine, 3,14-dihydroangustine and 3,14-dihydroangustoline were evaluated using human bladder carcinoma cells T-24 and EGF-dependent mouse keratinocytes MK. Only angustine and 3,14-dihydroangustine reached a micromolar range of inhibition, on the MK model (IC_{50} = 1.3 µM and 3.5 µM respectively), while all other assays led to at least 10-times higher values (Erdelmeier et al., 1992). The three compounds, together with analogous angustidine, were even less active on LNCaP and PC-3 human prostate cancer cells ($IC_{50} > 36$ µM in all cases). In addition, no selectivities were recorded vs. RWPE human normal prostate epithelial cell-lines (Liew et al., 2014). Another study regarding the potential of angustoline and naucleidinal reported the moderate activity of the latter on human prostate PC3, leukemic K562 and HL-60, lung A549 and gastro SGC-7901 cancer cell-lines (IC_{50} = 17.6 µM, 15.8 µM, 18.6 µM, 22.5 µM and 8.1 µM respectively), while the former was a weaker growth inhibition in all cases (Sun et al., 2008). Strictosamide was evaluated but proved to be a very weak cytotoxic agent in each cases ($IC_{50} > 100$ µM vs. both lung A549, lung MRC5, liver HepG2, breast MCF-7 and leukemic K562 cancer cells; Mesia et al., 2010; Costa et al., 2015; Li et al., 2015). A series of quinovic acid glycosides and cadambine acid, from *N. diderrichii*, were also tested against human monocytes, but revealed very low cytotoxicity in each case, with IC_{50} above 200 µM (Di Giorgio et al., 2006).

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

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

Table 23
Reported toxic activities of African *Nauclea* species extracts.

Species	*Plant parts*	*Extracts*	*References*
N. diderrichii	SB	MeOH : H_2O (80 : 80) (m)	Liu et al. (2011)
N. diderrichii	SB	MeOH (m)	Ogbole et al. (2016)
N. latifolia	SB	EtOH : H_2O	Gueye-Sanokho et al. (1993)
N. latifolia	nd	$CHCl_3$	Traore et al. (2000)
N. latifolia	L	EtOH (d)	Akpanabiatu et al. (2005b)
N. latifolia	SB	MeOH	Otimenyin and Uguru (2007)
N. latifolia	SB	MeOH : H_2O (80 : 80) (m)	Liu et al. (2011)
N. latifolia	S	Aq (m)	Arise et al. (2012)
N. latifolia	L	MeOH (m)	Akinloye and Olaniyi (2012)
N. latifolia	SB	Aq (m)	Kouadio et al. (2014)
N. latifolia	L	EtOH : H_2O (70 : 30) (d)	Solomon et al. (2014a, 2014b)
N. latifolia	L	Aq (d)	Magili et al. (2014)
N. latifolia	RB, L	MeOH (d)	Oise et al. (2014)
N. latifolia	SB, RB, L, F	EtOH : H_2O (70 : 30) (m)	Ogenyi et al. (2015)
N. pobeguinii	SB	MeOH : H_2O (80 : 20) (m)	Mesia et al. (2005, 2010)
N. pobeguinii	SB	MeOH : H_2O (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).

6. Conclusion

The genus *Nauclea,* used in sub-Saharan Africa since decades in traditional medicine, 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. Thus, the consequent amount of bibliographical data clearly needed a compilation and critical analysis, as 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 highly prevalent 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 whereas *N. nyasica*, *N. gilletii*, *N. vandergutchii* and *N. xanthoxylon* rarely occurred in literature. Despite the insufficient quality of some pharmacological evaluation — e.g. lack of internal control, standardization — studies conducted tend to validate traditional uses. However, it should be noted that the aqueous macerate, the major preparation mode for oral intake, was not always identified as the most efficient extracting mode. The genus *Nauclea* has been involved in three improved traditional medicines indicated for malaria. One of them, a combination of *N. latifolia* and *Cassia occidentalis*, is already used in D.R. Congo under the name Manalaria®. The two others, extracts of *N. pobeguinii* and *N. latifolia* named respectively PR 259 CT1 and NIPRD AM1®, are still under clinical development in Nigeria since several years.

The phytochemistry of the genus *Nauclea* has been extensively described and various classes of compounds are reported in several species. Among these, indoloquinolizidines alkaloids appeared to be characteristic of this genus, with numerous reported biological activities. However, these compounds often occur at very low concentration, and their activity level do probably not significantly contribute to the pharmacological properties of the corresponding extracts, except for strictosamide which is present in far more amounts in the *Nauclea* genus. Most of the time, the activities of the studied extracts are thus far from any molecular rationalization of the observed effects, which are probably the result of either a combination of bioactive molecules or a synergetic effect. 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 taken 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 concerning their geographical distribution, traditional uses, pharmacological activities and chemical composition.

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