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Nauclea latifolia: A Medicinal, Economic and Pharmacological Review

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Abstract **Objectives:** *Nauclea latifolia* Smith (family: Rubiaceae) is a valuable medicinal plant that is widespread in the humid tropical rainforest or in savannah woodland zone of West and Central Africa. Different parts of the plant possess remarkable therapeutic actions that can support the traditional usage of this plant in the treatment of several ailments. The plant was described with the origin, distribution, and its local uses. This review was focused on its ethno medicinal and economic uses, as well as its phytochemical and pharmacologic activities. **Materials and Methods:** The scientific resources including ScopeMed, PubMed, Scopus, Hinari and Google scholar were searched using key words such as: *Nauclea latifolia,* ethno medicinal uses, non-medicinal uses, economic value, phytochemistry, pharmacological activities. **Results:** *N. latifolia* and its phytochemical constituents, showed positive effects in prevention or curing many ailments through various mechanisms such as antioxidative, anti-inflammatory, anti-hypertensive, antisecretory, and antiulcerogenic effects. **Conclusions:** This review has scientifically justified some traditional uses of *N. latifolia* in the management of human diseases. Hence, exploiting all the qualities of this plant may offer solutions to some prevailing clinical conditions; since it is becoming obvious that the natural vegetation around us is enriched with solutions to most of our health challenges and the extent to which we discover it have great implications to dealing with these challenges.

Keywords *Nauclea latifolia*, Phytochemistry, Ethno medicinal uses, Pharmacological activity, Economic value

1. Introduction

African plants constitute a rich and still underexplored source of natural products of potential medical interest. According to World Health Organization (WHO), an approximately 80% of world population relies on herbal preparations as their primary source of healthcare (Kumara, 2001). It is estimated that some 20,000 species of higher plants are used medicinally throughout the world (Tagboto and Townson, 2001). Millions of Africans rely on these herbal preparations for their primary health care (McCaleb, 2000). Plants have provided the basis for traditional treatment for different types of diseases and still offer an enormous potential source of new chemotherapeutic agents. A plant becomes a medicinal plant only when its biological activity has been ethno botanically reported or scientifically established (Elujoba, 1995). Plants and their derived products from the outset have also served as veritable sources of food for humans and animals (Ogbonnia *et al*., 2011).

Nauclea latifolia smith (family: Rubiaceae) is a spreading, evergreen, multi-stemmed shrub or small tree native to tropical Africa and Asia (Gidado *et al*., 2005). Nauclea *latifolia* is a valuable medicinal plant that is widespread in the humid tropical rainforest zone or in savannah woodlands of West and Central Africa. It is known as African peach and may be used for traditional medicinal practices of the East and West African sub-regions of continental Africa (Dalziel, 1957) where various extracts of the plant are used for the therapeutic management of malaria (Gamaniel *et al*., 1995); hypertension (Akubue and Mittal, 1982); prolonged menstrual flow (Elujoba, 1995); cough, gonorrhoea, stomach disorders, dysentery, ulcers and liver ailments (Traore *et al*., 2000).

The present review of *Nauclea latifolia* deals with its origin, distribution, ethnomedicinal, economic, phytochemical and results of reported research findings on its medicinal properties.

2. Origin and Distribution

Nauclea latifolia (*N. Latifolia*) is native to Africa and Asia (Gidado *et al*., 2005). It is widely distributed throughout the forest and tropical forests of Benin, Burkina Faso, Cameroon, Democratic Republic of Congo, Ghana and Nigeria (Lamidi *et al*., 1993). *N. latifolia* is commonly found in Senegal, Cameroon, Nigeria, and as far as Sudan, tropical and Southern Africa (Michel, 2004). In Nigeria, it is found in areas like Kontagora, Abuja, Shaki, Akwa Ibom, Cross River,

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Enugu, Abakaliki and other parts of the country.

Its generic name is derived from the Greek word "sarco" (fleshy) and "cephalus" (headed) in reference to the flowers. The specific epithet is derived from the Latin word "lati" (broad) and "folius" (leaved) (Arbonnier, 2000). Three other related species *N. pobeguini, N. diderichii,* and *N. vanderguchtii* are forest trees. *N. Diderichii* is planted in Omo forest reserve, Nigeria. In the folk medicine, the species *N. diderichii* and *N. orientalis* are used in the same way as *N. latifolia.* Some of them, including *N. latifolia*, are used in sub-Saharan traditional system of medicine to treat several diseases suggesting that they may represent a natural source of pharmacologically active substances (Karou *et al*., 2011).

N. latifolia is commonly known as "Ubulu inu" among the Igbos in the Eastern part of Nigeria; as "Tafashiya" or "Marga" or "tabashiya" or "tuwon biri" among the Hausas in the Northern part of Nigeria; as "Egbesi" among the Yoruba in the Western part of Nigeria, "Mbom-ibong'' in Ibibio and as "Itu" among the Itsekiri, mahyann (Fali) language. The common name include Pin cushion tree (English) or African peach or scille maritime (French) (Arise *et al*., 2012).

3. Morphological Characteristic

N. latifolia belongs to Rubiaceae, a large family comprising more than 630 genera and about 13000 species of plants. It is a spreading, evergreen, multi-stemmed shrub or small tree. It bears an interesting flower, large red ball fruit with long projecting stamens. It grows up to an altitude of 200 m. It grows rarely over 20ft high, bole crooked; or a larger tree over 100ft high and 8ft girth, in closed forest. The plant has rough bark and leaves that measure 7 by 4-5 inches (Duke, 2008).

The leaves are glabrous, opposite, rounded-ovate, glossy green with tufts of hairs. The fruits are usually fleshy, shallow-pitched, with numerous embedded seeds surrounded by a pink edible, sweet- sour pulp (a syncarp up to 3 inches in diameter). The fruits are not appealing but edible. The seeds are usually small, ovoid, numerous and brownish with a pleasant taste but could be emetic if taken in excess (Iwu, 1993).

The stem is cracked dark grey brown with fibrous reddish slash. It is multi-stemmed and has an open canopy flowers with terminal spherical head like cymes of small whitish flowers. Flower head is up to 2mm in diameter, sweet scented and sought by bees. The flowers are joined with their calyces (Michel, 2004). The tree flowers from April to June while the fruits ripen from July to September.

4. Taxonomy of *Nauclea latifolia*

➢ **Botanical name:** *Nauclea latifolia Smith*

Six taxonomy levels for *Nauclea latifolia*:

- Kingdom: Plantae
- Phylum: Tracheophyta
- Class: Magnoliopsida
- Order: Gentianales
- Family: Rubiaceae
- Genus: Nauclea L.

Source: Adapted from Global Biodiversity Information Facility (**GBIF**)

Preferred name: *Nauclea latifolia* Sm.

Synonyms: *Sarcocephalus latifolius* (Sm.) E.A. Bruce

English names: African peach, Pin cushion tree, Guinea peach, Sierra Leone peach, Bishop's head.

Vernacular names:

French- Scille maritime, oignon marine, medicinal squill

African vernacular names:

Cameroon (Tupuri language) - Koumkouma

Hausa- Tafashiya, tashiyaigia, tafiyaigia, Marga, tabashiya, tuwon biri

Igede (Benue) - Uche

Igbo- Ubulu inu, Uvuru-ilu

Yoruba- Egbesi

Ibibio- Mbom-ibong

Itsekiri- Itu

Kilba- Molsa

Trade name: Opepe

Source: Adapted from Arise *et al.,* 2012

Figure 1. Diagram showing the leaves, fruit and flower of *Nauclea latifolia Smith* (Fern, 2014)

5. Ethnomedicinal Uses

N. latifolia herbal remedies have been commonly used in various cultures throughout recorded history and still serve as the main means of therapeutic medical treatment (Deeni and Hussain, 1991). In many African countries, the plant is commonly used as a remedy for diarrhea, pain, dental caries, septic mouth, and diabetes (Gidado *et al*., 2004). Other uses include treatment of malaria, leprosy, debility, hypertension, gastrointestinal disorders, prolonged menstrual flow and sleeping sickness (Kerharo, 1974; Elujoba, 1995).

In Nigerian traditional medicine, the stem bark, and roots

of the plant are used against fever, jaundice, malaria, diarrhoea, dysentery, hypertension and diabetes (Okwori *et al*., 2008). The fruits are sometimes used in the treatment of piles and dysentery (Reitman *et al*., 1957). In addition, the plant is used in the treatment of sleeping sickness and prolonged menstrual flow (Elujoba, 1995). The plant is known as 'Africa cinchona' or 'Africa quinine' because of its reported anti-malarial activity (Abbiw 1990). In Northern Nigeria, a cold infusion of the stem bark is taken as a diuretic and anti-helmintic (Ademola *et al*., 2007). The Fulanis in Nigeria use the leaf extract to regularly deworm animals (Adebowale *et al*., 1993). In Kano (Nigeria), the plant is used as a chewing stick and as a remedy against stomach ache and tuberculosis (Deeni & Hussain 1991). The roots and major ingredients of *N. latifolia* are used in treatment of respiratory illnesses such as tuberculosis, asthma, bronchitis, cough and cold in Niger State (Abdullahi *et al*., 2007). In Hong, Adamawa State, concoctions, infusions, and decoctions from stem bark and roots are used against jaundice, fever, stomach ache, and dysentery (Maitera *et al*., 2011). In Benue State, decoction from the leaf is used to treat fever, filariasis, and chicken pox while the stem bark is used to treat infertility.

Table 1. Ethnomedicinal uses of different morphological parts of *Nauclea latifolia*

Part	Medicinal uses	References
Root	It is used in treatment of malaria, as a tonic and remedy for fever, toothaches, dental caries, septic mouth, cough, stomach disorders, diarrhoea, dysentery, treatment of gonorrhoea and wound. It is used in pyrexia-induced cold extremities, treating pain in legs and arms, relieving bronchitis; as antidiabetic and antiparasitic. It is also acts as a stimulant and restorative, aphrodisiac and analgesic. It is used to treat jaundice, loss of appetite, rheumatism, hepatitis, yellow fever, diabetes and hypertension. It is also used for treatment of respiratory illnesses such as tuberculosis, asthma, as an antidepressant, purgative, in treatment of preterm contraction in pregnant women and to induce abortion.	Vasileva, 1969, Oye, 1990; Deeni and Hussain, 1991; Lamidi *et al*., 1995; Adjanohoun *et al*., 1996; Pedro and Antonio, 1998; Arbonnier, 2000; Gidado *et al*; 2005; Okwori *et al*., 2008; Duke, 2008.
Stem	It is used in the treatment of stomach pain, constipation, fever, diarrhoea. It serves as an antiparasitic, antidiabetic antihypertensive, as well as diuretic and antihelmintic agents. It also has a role in treatment of jaundice, dysentery, malaria, preterm contraction in pregnant women and serves as an aphrodisiac.	Deeni and Hussain, 1991; Esimore *et al*., 2003; Etukudoh, 2003; Ademola *et al*., 2007; Okwori *et al*., 2008; Duke, 2008.
Bark	It is used in treatment of malaria, wounds, cough and gonorrhoea. It serves as a tonic and remedy for fever, toothaches, dental caries, septic mouth and stomach disorders such as diarrhoea, dysentery. It is also used in treatment of gonorrhoea and wound, as well as in treatment of preterm contraction in pregnant women	Oye, 1990; Lamidi *et al*., 1995, Pedro and Antonio, 1998; Duke, 2008; Isah *et al*., 2012.
leaves	It serves as antimalaria, antidiabetic and antipyretic. It is used in the treatment of stomach ache, constipation, fever, and diarrhoea, sores, anxiety, depression and epilepsy	Abbiw, 1990; Pedro and Antonio, 1998; Esimore *et al*., 2003; Orwa *et al*., 2009
Fruit	It is used in the treatment of cough, piles, dysentery, abdominal colic, emesis, menstrual disorder and human immune deficiency virus infection	Gill, 1992; Hussein *et al.,* 1999; Orwa *et al*., 2009.
Wood	Stimulant and tonic	Orwa *et al*., 2009.

Table 2. Worldwide ethnomedicinal uses of *Nauclea latifolia*

Country	Usage	References
West and south Africa	It is used for the treatment of malaria, stomach ache, fever, diarrhoea, nematode infections	Deeni and Hussain, 1991.
Sudan	It is used to treat sores and gonorrhoea	Irvine, 1961.
Ghana	It is used to treat sores and gonorrhoea	Irvine, 1961.
Ivory Coast	It is used to treat sores and gonorrhoea	Irvine, 1961.
Nigeria	It is used to treat sores and gonorrhoea, fever, jaundice, malaria, measles, hypertension, dysentery, diabetes, respiratory illness, sleeping sickness and prolonged menstrual flow. It also serves as diuretic, antihelmintic, antidepressants and analgesic.	Irvine, 1961; Elujoba, 1995; Abdullahi *et al*., 2007; Okwori *et al*., 2008.
Guinea	It serves as tonic, stimulant, and restorative. It is also used in the treatment of infectious diseases including sexually transmitted diseases	Cournal *et al*., 1998; Magassouba *et al*., 2007.
Cameroun	It is used to treat cerebral malaria, cerebral deficit, behavioural disturbance in mentally-retarded children, epilepsy, anxiety, depression, jaundice, yellow fever, rheumatism, abdominal pains, hepatitis, jaundice, loss of appetite, neuropathic pain remedy and for the treatment of headache, migraine, inflammatory pain and convulsion.	Adjanohoun *et al*., 1996; Taiwe *et al*., 2013.
Congo	It serves as an aphrodisiac and analgesic, used in treatment of sexual asthenia, diarrhoea	Tona *et al.*, 2000.
Mali	It is used to treat abdominal pains and malaria	Maiga *et al.*, 2005.

Table 3. Local uses of *Nauclea latifolia*

Morphological part	Non-Medicinal uses	References
Root	It is used as a dye and chewing stick	Gill, 1992.
Wood	It is termite resistant and used as a live stakes in farm. It is also used as fuel	Esimore *et al*., 2003.
Tree	It offers shade and acts as windbreak. It is also used as live stake to provide barriers in farms	Deeni and Hussain, 1991.
Twig	It is used as chewing sticks	Burkil, 1985.
Shoots	It serves as food for livestock	Anowi *et al*., 2012.
Leaves	It serves as food for livestock. It is also used as mulch	Anowi *et al*., 2012.
Seeds	It is eaten by baboons	Anowi *et al*; 2012.
Fruits	Key source of food for baboons, livestock, reptiles, birds, and man. A soft drink is obtained from the fruit	Omale and Ugbede, 2011; Deeni and Hussain, 1991.
Flower	The flower heads are cooked and eaten as a vegetable	Deeni and Hussain, 1991.

Table 4. Chemical composition of various parts of *Nauclea latifolia smith*

Parts	Constituents	References
Root bark	Tannins, flavonoids, alkaloids, saponins, cardiac glycosides, terpenoids, steroids, carbohydrates, glycoalkaloids (3-a-dihydrocadambine, hydrocyanic acid, indolo-quinolizidine (anguistine, angustoline)	Hottellier *et al.*, 1975; Yesufu *et al*., 2010; Maitera *et al*., 2011; Egbung *et al*., 2013.
Stem bark	Alkaloids, cardiac glycosides, terpenes, saponins, tannins, flavonoids, anthraquinones, sterols, glycoalkaloids, hydrocyanic acid, phenols, resins, polyphenols, carotenoids, limonoids, xanthonoids, balsam, phlobatannins	Hotellier *et al*., 1979; Morah, 1995, Maitera *et al*., 2011; Anowi *et al.*, 2012; Udobre *et al.*, 2012; Egbung *et al*., 2013; Ikpeme *et al*., 2013; Ifemeje *et al*., 2014.
Leaves	Alkaloids, tannins, saponins, glycosides, anthraquinones, carbohydrates, flavonoids, phytates, isoflavonoid (Indicanine B and C), phlobatannins, cardenolides, phenols, terpenoids, cardiac glycoside,	Borrelli and Izzo, 2001; El-Mahmood *et al*., 2008; Ahuocha, 2010; Ogueke *et al*., 2011; Orole *et al*., 2013; Edet *et al*., 2013; Balogun *et al.*, 2015; Onu *et al*., 2015.
Fruits	Tannins, alkaloids, flavonoids, saponins, phytates, cyanogenic glycosides, phosphate, anthraquinones, coumarins, monoterpenes, fatty acid esters (palmitic acid, ethyl ester, isopalmitic acid, methyl ester, elaidic acid, methyl ester	Fadipe *et al*., 2013; Eze and Obinwa, 2014; Fadipe *et al*., 2014; Brown *et al*., 1997.
Root	Tannin, saponins, alkaloids, terpenes, cardiac glycosides, flavonoids, anthraquinones, sugars, indole alkaloids (strictosamide, vincosamide, pumiloside, quinovic acid glycoside), phenols	Nworgu *et al*., 2008; Taiwe *et al*., 2011; Manuela *et al*., 2013; Bamidele *et al*., 2014; Antia and Okon, 2014.
Bark	Monoterpenes indole alkaloids- naucleamides A-E	Shigemori *et al*., 2003.
Wood	Monoterpenes indole alkaloids- naucleamides A-E	Shigemori *et al*., 2003.

Among the Ibibios of South-South Nigeria, the stem bark either as an infusion or decoction is used as antimalaria, antipyretic and aphrodisiac. The root bark is used as tonic, antipyretic, antidepressant and analgesic. The leaf has the potential to relieve dysentery and diarrhoea (Etukudoh, 2003). The indigenous people of Abia State in South-East, Nigeria use it extensively for management and treatment of gastrointestinal ulcers (Alaribe *et al*., 2014). The traditional birth attendant in Nigeria have used the ethanolic extract of *N. latifolia* stem and root bark in arresting pre-term contraction in pregnant women (Duke, 2008). Parts of the plant are commonly prescribed traditionally as a remedy for diabetes mellitus (Akabue and Mittal, 1982; Boye, 1990). Nearly all the plant parts are useful in treatment of diseases (Arbonnier, 2000). However, the most frequently used plant parts are the roots, followed by the stem, bark, and leaves.

6. Non Medicinal Uses

N. latifolia is known for its non- medicinal applications. Commonly used parts of this plant include the leaves, roots, stem, and fruits. The vitamin and proximate results revealed a possible potential of the plant parts as component of animal feeds. The fruits serve as key source of food for the baboons, livestock, reptiles, birds, and man (Omale and Ugbede, 2011).

In Sudan, ripe fruits are eaten and soft drinks are prepared from these fruits while over-ripe fruits are sometimes dried and a powder is prepared from them and used as a base for soft drinks (Abdelmuti, 1991). The fruits of the plant are reportedly rich in vitamin C and this has made them a good source of fruit juice (Amoo and Lajide, 1999). Flower heads are cooked and eaten as a vegetable. Baboons eat and

disperse the seeds. Livestock eat shoots and leaves. It is commonly used by palm wine tappers as a preparative ("nche") for palm wine (Ogueke *et al*., 2011).

N. latifolia is suitable specie for planting schemes for conservation and soil stabilization. *The* tree offers shade and acts as a windbreak. It is used as a live stake to provide barriers in farms. The leaves are used as mulch. The wood of *N. latifolia* is termite resistant and is used as a live stakes in farms. The wood is used for fuel too. Small twigs are used as chewing sticks (Burkil, 1985; Esimore *et al*., 2003). A yellow dye is obtained from the roots. The root is also chewed as chewing stick (Gill, 1992).

7. Pharmacological Activities

Antiulcerative activity

Balogun *et al*., (2013) reported the anti-ulcer activity of aqueous leaf extract of *N. latifolia* against indomethacin-induced gastric ulcers in rats. The extract at 340 and 510mg/kg doses produced a greater protection than cimetidine (100mg/kg) against the indomethacin- induced gastric ulcer in rats. The study concluded that the extract possessed a significant and dose dependent anti-ulcer activity against experimentally induced gastric lesion and may justify its use as an anti-ulcerogenic agent.

In another study, Orole *et al.,* (2013) investigated the antiulcerogenic potential of ethanolic leaf extracts of *Kigelia africana, N. Latifolia,* and *Staudtia stipitata* on aspirin-induced ulcer in albino rats at doses of 150mg/kg, 300mg/kg, and 450mg/kg body weight. Ulcer index and acidity of the gastric contents were measured in the treated animal and compared to the control. Extract of *N. latifolia* at a concentration of 450 mg/kg body weight gave the best results with a significant decrease in ulcer index on aspirin-induced ulcerogenic animals compared to the reference drug (Cimetidine at 300mg/kg), while the leaf extracts of *S. stipitata* showed the least efficacy. The authors suggested that the extracts could be employed in the management of ulcer diseases caused by non steroidal anti-inflammatory drugs (NSAIDs).

Alaribe *et al.,* (2014) investigated the healing, cytoprotective and anti *H. pylori* activities of stem bark extract and butanol fraction (BNL) of *N. latifolia*. In this study, their ability to inhibit gastric lesions in histamine and aspirin-induced ulcer models in rats was assessed by recording their influence on pH, wall mucus, acidity and gastric acid output. The extract (50mg/kg and 100mg/kg) and BNL (50mg/kg) were administered daily for seven days for cytoprotective and healing studies. Cimetidine, omeprazole and misoprotol (20 mg/kg respectively) were used as reference drugs. The *in vitro* anti-Helicobacter pylori activities of the extract and BNL were also investigated using agar disk diffusion method. They significantly increased ulcer tolerant rate and healing rate compared to controls. Increase in pH in groups treated with the extract and BNL was also observed. The results showed that the test extract and BNL have more cyto protective than healing properties. Results of anti- *H. pylori* studies showed the minimum inhibitory concentration (MIC) for crude extract to be 25 mg/ml while the minimum bactericidal concentration (MBC) is 100mg/ml. The authors concluded that *N. latifolia* possessed significant cyto-protective activities on aspirin and histamine induced gastric lesion and promising anti *H. pylori* effect thus justifying its use in folkloric medicine as antiulcer agent.

In a recent study, the anti-ulcerogenic effects of aqueous stem bark extract of *N. latifolia* using ethanol/HCI and indomethacin as the ulcerogens was conducted (Balogun *et al.,* 2016). The effect of the extract on gastric mucous secretion was also investigated. The extract was administered orally at the doses of 100 and 200 mg/kg b. wt. for the experimental groups while the control and reference groups received distilled water (2 ml/kg, p.o) and omeprazole (20 mg/kg, p.o) respectively. The results showed that the extract significantly ($p < 0.05$) reduced the ulcer index from (4.55 ± 1.45 to 1.20 ± 0.19) and from (4.20 ± 0.72 to 0.94 ± 2.51) in the ethanol/HCI and indomethacin induced ulceration respectively. The extract also significantly ($p < 0.05$) increased the gastric mucous secretion in a dose-dependent manner. The authors concluded that *N. latifolia* stem bark extract possessed significant anti-ulcer effects which might be due to its ability to increase gastric mucous secretion.

Antisecretory activity

Balogun *et al.,* (2014) further investigated the effects of aqueous leaf extract of *N. latifolia* on gastric acid secretion as the possible mechanism of its anti-ulcer actions in male albino rats. In the animal model studied, gastric mucosal injury was induced using indomethacin (30mg/kg, p.o) 60 minutes post administration of the extract at the doses of 100, 200 and 400 mg/kg for the experimental groups while the control and reference groups received distilled water (2 ml/kg, p.o) and cimetidine (32 mg/kg, p.o) respectively. Thereafter, gastric acid output was measured by the continuous perfusion of rat's stomach under anaesthesia with normal saline at the rate of 1 ml/min. The result showed that rats pre-treated with *N. latifolia* exhibited significant ($P<0.05$), and dose-dependent inhibition of indomethacin-induced gastric ulceration. A significant decrease in gastric acid secretion was produced by the extract at all doses studied. The study also concluded that aqueous extract of *N. latifolia* significantly reduced gastric acid secretion in indomethacin-induced gastric ulceration by inhibiting histamine-stimulated gastric acid secretion probably by occupying H_2 receptors in rats.

In a similar work, Balogun *et al.*, (2015) evaluated the anti-ulcerogenic and gastric anti-secretory effects of methanol leaf extract of *N. latifolia* in indomethacin-induced gastric ulceration in rats. The extract was administered orally at the doses of 200, 400 and 800 mg/kg body weight for the experimental groups while the control and reference groups received distilled water (2ml/kg, p.o) and cimetidine (100

mg/kg, p.o) respectively. The extract (200, 400, and 800 mg/kg) exhibited significant ($P<0.05$), and dose-dependent inhibition of indomethacin-induced gastric ulceration that seemed to be stronger than cimetidine (100 mg/kg). A significant decrease in gastric acid secretion with concomitant increase in intragastric mucous secretion was produced by the extract at all doses studied. The results suggested that the extract possessed a significant gastro protective effect in indomethacin-induced gastric lesions.

Antimicrobial activity

El-Mahmood *et al.,* (2008) carried out comparative studies of extracts of leaves, barks and roots of *N. latifolia* and *Daniella oliveri* with respect to their antibacterial properties. The antibacterial screening of the water and ethanolic extracts of the various plant materials were carried out against pathogenic bacteria including *Pseudomonas aeruginosa, Klebsiealla pneumonia, Escherichia coli, Staphylococcus aureus* and *Shigella dysenteriae* as described by Lino and Deogracious (2006) and Akoma *et al.,* (2002). Ethanolic extracts were more potent than aqueous extracts and activity were concentration dependent. The Gram positive bacteria were more sensitive to the ethanolic extracts of both plants.

In vitro effect of *N. latifolia* extract in hot water, cold water, petroleum ether and chloroform at concentration of 200, 150, 100, and 50% were tested on some pathogenic bacteria such as *Staphylococcus aureus, Escherichia coli, Salmonella typhi* and *Pseudomonas aeruginosa* (Okwori *et al.*, 2008). Using agar diffusion punch hole method, both the aqueous and alcoholic extracts of the leaves and roots showed appreciable inhibitory effect when compared to the positive control on *S. aureus* and *P. aeruginosa* while *S. typhi and E. coli* were resistant to the extracts. Using serial doubling dilution, the minimum inhibitory concentration (MIC) was determined. The minimum bacteria concentration was determined by plating various dilutions of the extracts without turbidity. Aqueous and alcoholic extracts of *N. latifolia* showed inhibitory and bactericidal activity on the test organisms. The alcoholic extracts showed larger zone of inhibition on the test organisms. The alcohol leaf extracts showed a higher percentage of growth inhibition when compared to the positive control. The MIC ranges from 6.25 – 150 mg/ml on S. aureus and 12.5 – 150 mg/ml for P. aeruginosa. The MBC ranges from 100 – 150 mg/ml.

In vitro effect of *N. latifolia* leaf extract in ethanol, hot water and cold water at concentrations of 400, 200, 100 and 50mg/ml were tested on some pathogenic bacteria such as *Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, Salmonella typhi* and *Pseudomonas aeruginosa* and fungal strains such as *Candida albicans* and *Aspergillus flavus* (Ahuocha, 2010). Using agar well diffusion method, both the ethanolic and aqueous extracts of the leaves showed visible inhibitory effect when compared to the positive control. The ethanolic and hot water extracts of *N. latifolia* showed zones of inhibition ranging from 12 – 26mm and 10 – 26mm on *S. aureus* and *P. aeruginosa* respectively at concentrations of 50 – 400mg/ml. The ethanolic extract was observed to be more potent. The cold water extract showed activity (7mm) against only *P. aeruginosa* at concentrations of 400mg/ml and 200mg/ml. No zones of inhibition were observed on both ethanolic and aqueous leaf extracts on the fungal organisms at all concentrations. Aqueous and ethanolic extracts showed bacteristatic and bactericidal activity on the test bacterial organisms.

Meanwhile, Ogueke *et al.*, (2011) investigated the antibacterial potentials of hot and cold ethanol leaf extract of *N. latifolia*. The Agar diffusion method was used for the antibacterial assay at different concentrations on *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Salmonella typhi.* The results obtained from the study showed that in general the hot ethanol extracts produced greater inhibitory effect on the isolates than the cold ethanol extracts. The growth of S. typhi was not inhibited by the extract.

Maitera *et al.*, (2011) also reported the antibacterial activity of methanol and aqueous leaves, stem-bark and roots extracts of *N. latifolia*. Disc diffusion method was used in determining the antibacterial activity (*Escherichia coli, Streptococcus pneumonia, Shigella, dysenteriae*, and *Staphylococcus aureus*). The results showed that methanol extract of the leaves and stem bark exhibited antimicrobial activity against the entire microorganisms tested; with *E coli* being most susceptible while *S. aureus* was least susceptible. Water extract of leaves was found to have antimicrobial activity against *S. pneumonia* and *S. aureus*. All tested microorganism were not sensitive to the water extract of the stem bark and the n-hexane. The results of this study indicated that the different plant parts posses a wide range of antimicrobial activity against the microorganisms tested.

Anowi *et al*., (2012) also evaluated the antimicrobial activity of ethyl acetate crude extracts of *N. latifolia* stem bark and the standards (augmentin; an antibacterial agent and ketoconazole; an antifungal agent) against Gram positive bacteria (*Staphylococcus aereus* and *Bacillus subtilis*); Gram negative bacteria (*Escherichia coli, Pseudomonas aeruginosa* and *Shigella dysentariae*) and fungal species (*Candida albicans and Aspergillus niger*) using agar diffusion method at the minimum inhibitory concentration. The results showed that ethyl acetate extract of the stem bark exhibited activity against *E coli, S dysentariae, S aereus, B subtilis and A niger,* with minimum inhibitory concentration (MIC) ranging from 2.4 mg/dl – 20.89 mg/ml. The extract also showed significant effectiveness against *Pseudomonas aeruginosa* when compared to the standard. It was then concluded that the stem bark of *N. latifolia* possessed broad spectrum antimicrobial activities and may be useful in the formulation of antimicrobial agent that could be used for the treatment of microbial infections of different origins. Further bioassay targeted technique studies on the crude extract for purification and identification of the constituents with antimicrobial properties as well as its effect on more pathogenic organisms are recommended.

Fadipe *et al.*, (2013) studied the *in-vitro* antibacterial activity of the petroleum ether and methanol extracts, portions and sub-portions of the ripe and unripe fruits of *N. latifolia.* Antibacterial activity of the extracts (100 mg/ml), portions (50 mg/ml) and sub-portions (50 mg/ml) in comparison with standard drugs (1 mg/ml) against two Gram-positive (*Bacillus subtilis* and *Staphylococcus aureus*) and four Gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Salmonella typhi*) using the agar-well diffusion method revealed higher zones of inhibition, higher calculated percent activities (A%), higher calculated bacterial susceptibility (BSI), lower minimum inhibition concentrations (MICs) and minimum bactericidal concentrations (MBCs) for the extract/sub-portions of the unripe fruits than the extracts/portions/sub-portions of the ripe fruits, an indication that the unripe fruits exhibited better antibacterial efficacy against the tested strains. The diethyl ether (MuiD) and ethyl acetate (MuiE) sub-portions of the unripe fruits displayed broad spectrum activity than chloramphenicol and tetracycline supporting their use in the treatment of dysentery and diarrhoea.

Ifemeje et al., (2014) investigated the in vitro antibacterial activity of the ethanolic extract of the stem bark of Entada africana Guill. & Perr. and Sarcocephalus latifolus, on Staphylococcus aureus, Salmonella typhi, Escherichia coli and Bacillus subtilis. Agar well diffusion technique was used to screen the extracts for antibacterial activity. MIC and MBC for the various extracts were determined by the tube dilution technique. Ciprofloxacin, a standard antibiotic was used as control. The results revealed that the ethanolic extract of E. africana inhibited the growth of S. typhi and B. subtilis significantly while that of S. latifolius inhibited the growth of E. coli and B. subtilis significantly with the zones of inhibition ranging from 12.00±0.02 to 0.80±0.01. The MIC and MBC (minimum bactericidal concentration) for the organisms were at 5 mg/ml and 10 mg/ml. The ethanolic extract of the stem bark of the plant samples exhibited antibacterial activity and thus could serve as a source for useful antibacterial drugs.

Bamidele *et al.,* (2014) evaluated the *in vitro* antibacterial activity of three plants extract *Abrus precatorius*, *Croton penduliflorus* (Seeds) and *N. latifolia* (Root) on *Escherichia coli, Klebsiella pneumonia* and *Enterococcus faecalis* using agar diffusion method. Twelve extracts consisting of hot ethanol, cold ethanol, hot water and cold water were prepared. Efficacy was assessed by measuring the diameter of zone of inhibition around the colonies on Muller Hilton agar medium. *E. coli* showed the highest susceptibility to all plant extracts this was followed by *E. faecalis. K. pneumonia* showed the least susceptibility to all the extracts. The cold ethanolic extracts of the plants showed the highest susceptibility while the other extracts exhibited variable antibacterial activities. The minimum inhibitory concentration (MIC) of the eight most active extracts ranged between 3.025mg/ml to 50mg/ml while minimum bactericidal concentration (MBC) was between 6.25mg/ml - 25mg/ml. Commonly used antibiotics such as Augmentin and Amoxillin showed low sensitivity as compared to the extracts with varying inhibition zone of 0-4mm. This *in vitro* study demonstrated that folk medicine in addition to being cheaper could be effective as modern medicine in combating pathogenic microorganisms.

Anti-viral activity

Manuela *et al.,* (2013) reported the in vitro anti-herpes simplex virus activity of CH_2CL_2/MeOH crude extract of the root of *N. latifolia*. The anti-HSV-2 activity was assayed in vitro by plaque reduction and virus yield assays and the major mechanism of action was investigated by virucidal and time of addition assays. The result showed that *N. latifolia* crude extract inhibited both acyclovir sensitive and acyclovir resistant HSV-2 strains, with inhibitory concentration producing 50% reduction in plaque formation (IC50) IC_{50} values of 5.38µg/ml and 7.17µg/ml respectively. The extract was found to be most active when added post-infection, with IC50 of 3.63µg/ml. The virucidal assays ruled out the possibility that the antiviral activity of the extract was exerted by a direct inactivation of the virus particle. Further work remains to be done in order to isolate the active principle and elucidate its mechanism of action or to develop a phyto-drug from *N. latifolia* CH_2CL_2/MeOH extract.

Ethanolic and aqueous leaf extracts of *N. latifolia* were also shown to possess antiviral activity on Newcastle disease virus (wild type) in embryonated chicken eggs (Onu *et al.*, 2015). The ethanolic extract of the plant possessed greater toxicity and antiviral effects than the hot water extract. The authors suggested that *N. latifolia* could be used in the prophylaxis of Newcastle disease.

Anti-helmintic activity

Onyeyili *et al.,* (2001) assessed the antihelmintic efficacy of stem bark aqueous extract of *N. latifolia* in sheep with natural acute/sub-acute parasitic gastro-enteritis. Graded doses of the extract (400, 800 and 1600 mg/kg) administered orally for 5 consecutive days, significantly reduced faecal egg counts in infected animals. The percentage reduction (93.8%) by 1600 mg/kg of the extract was comparable to that of 5 mg/kg of albendazole (94.1%). The administration of the extract further resulted in improved haemoglobin and leucocytosis values in worm-infected sheep.

In another study, Ademola *et al.,* (2007) examined the possible direct effects of aqueous and ethanolic leaf extracts of *N latifolia* on different gastrointestinal nematodes of sheep. A larval development assay was used to investigate *in vitro,* the effect of the extracts of *N. latifolia* towards strongyles larvae while the development and survival of infective larvae (L_3) was assessed *in vivo* using faecal egg count per gram after oral administration of the extracts at a dose rate of 125 mg/kg, 250 mg/kg, and 500 mg/kg body weight.

The extracts were found to decrease the survival rate of larvae. The aqueous extract demonstrated a lower activity (0.704mg/ml) compared to the ethanolic extract (0,650mg/ml). Faecal egg counts (FEC) on day 12 after

treatment showed that the extracts were more effective compared to control at 500mg/kg against *Haemonchus spp, Trichostrongylus spp*, *Strongyloides spp*; at 250mg/kg against *Trichuris spp* and ineffective against *Oesophagostomum spp*. The authors suggested that the extracts showed broad spectrum action against sheep nematodes and thus could be significant in antihelmintic therapy in livestock.

Antiplasmodial activity

Benoit-Vical *et al.,* (1998) studied the *in vitro* activity of aqueous stem and root *N. latifolia* extracts on two strains of *Plasmodium falciparum*: FcB1-Colombia (chloroquine-resistant) and a Nigerian strain (chloroquine-sensitive) using both visually and radioactive methods. The visual analysis allowed determination of the time of extract action on the erythrocytic cycle, as well as the parasitic stage of most inhibitory effect. Similar results were obtained applying fresh, frozen or lyophilized extracts and the authors concluded that the extracts inhibited *P. falciparum* (FcB1 strain) mainly at the end of the erythrocytic cycle (32nd to 48th hour).

Ettenbong *et al.*, (2015) reported the in vivo antiplasmodial activities of the ethanolic extract and its fractions (n-hexane, chloroform, ethyl acetate, butanol, aqueous) of the stem bark in plasmodium berghei infected mice. The extract at doses (100, 200 and 300mg/kg) and fractions (200 mg/kg) were orally administered to the rats. Antiplasmodial activities were screened using 4-day suppressive, 7-day curative and repository tests. The extract exhibited significant and dose-dependent antiplasmodial activity in the suppressive, repository and curative tests. The aqueous fraction had the highest percentage chemo suppressive effect (67.71%). This discovery has confirmed the antimalaria potential of this plant. Further investigation to identify the phytochemical components responsible for this effect is required.

Antitrypanosomal activity

In vitro antitrypanosomal activity of methanolic and aqueous extracts of stem bark extracts of *N. latifolia* was evaluated on *Trypanosoma congolense* (Maikai and Kobo, 2008). In this study, blood obtained from highly infected mice with *T. congolense* (10^7) was incubated with methanolic and aqueous extracts at 20 mg, 10 mg and 5 mg/ml and Diminivet^R (a standard drug) at 10 mg, 200 and 50µg/ml in a 96 well microtiter plate. The extracts had antitrypanosomal activity at 20mg/ml compared to the standard drug at 10mg/ml. Further purification of the extracts could lead to isolation of purer compounds with increased activity like the standard drug.

Antioxidant activity

Hot water extracts of the leaves and fruits of *N. latifolia* were shown to possess antioxidant activity from 1-diphenyl-2-picrylhydrazyl (DPPH) scavenging ability, ferric reducing antioxidant power (FRAP), Trolox equivalence antioxidant capacity (TEAC), and oxygen radical absorbance capacity (ORAC) assays (Ademola *et al.,* 2014). The aqueous leaf extract was found to contain higher level of total polyphenols (11.63 ± 0.023mg GAE/g), flavanol (1.45 ± 0.10 mg CE/g), and flavonol (2.22 ± 0.37mg QE/g) than the extract of the fruits with values of 1.75 ± 0.02 mg GAE/g (total polyphenol), 0.15 ± 0.01mg CE/g (flavanol), and 1.00 ± 0.13mg QE/g (flavonol). Similarly, the aqueous extract of the leaves also exhibited higher DPPH (IC50 20.64mg/mL), FRAP (86.10 ± 3.46 μmol AAE/g), TEAC (94.83 ± 3.57 μmol TE/g), and ORAC (196.55 ± 0.073 μmol TE/g) than the extract of the fruits with DPPH (IC50 120.33mg/mL), FRAP (12.23 ± 0.40 μmol AAE/g), TEAC (12.48 ± 0.21 μmol TE/g), and ORAC (58.88 ± 0.073 μmol TE/g). These results showed that *N. latifolia* had strong antioxidant potentials with the leaves demonstrating higher *in vitro* antioxidant activities than the fruits and this could be responsible for the medicinal properties of this plant.

Anti-diarrhoeal activity

Owolabi *et al*., (2010) reported the ant diarrheal activity of ethanolic root bark extract of *N. latifolia* by investigating castor oil-induced diarrhoea and small intestinal motility in mice. Its inhibitory effect on intestinal transit and isolated ileum were also investigated in an attempt to provide scientific justification or (otherwise) for its folkloric use. The mice were divided into five experimental groups. Diarrhoea was induced by administering 0.3 mL of castor oil orally to mice (Awouters *et al.,* 1974). Small intestinal motility was evaluated by feeding the mice charcoal meal. Groups 2, 3 and 4 received the extract orally (125, 250 and 500 mg/kg respectively) while group 5 received atropine (0.2 mg/kg) 30 min before castor oil administration. Onset of diarrhoea and diarrhoea score were observed for a period of 3 h. The extract produced a significant dose dependent reduction in frequency and severity of diarrhoea induced by castor oil. The extract at all doses inhibited the propulsive movement of the charcoal meal along the small intestine by 63.94%, 67.82% and 72.54% respectively, compared to the control and 70.0% for atropine. The findings suggested that ethanolic root bark extract of *N. latifolia* possessed significant and dose-dependent ant diarrhoeal activity on gastrointestinal functions, gastrointestinal propulsion, and antispasmodic effect as a known cholinergic antagonist like atropine. This thus provides the scientific justification and basis for its folkloric use in the treatment of diarrhoea.

Anti-hypertensive activity

Nworgu *et al.*, (2008) studied the blood pressure lowering effect of ethanolic root extract of *N latifolia* in normotensive and hypertensive rats. The crude ethanolic extract was dissolved in 50% dimethylsulfoxide (DMSO) before administration to the rats. The effect of 50% DMSO alone followed by graded doses (2.5-20mg/kg) of the extract on the basal blood pressure were measured. The effects of a specific dose of the extract before and after administration of 1mg/kg each of atropine and promethazine were also noted. Cannulated carotid artery was connected to a Bentley

physiological pressure transducer for blood pressure and heart rate recording. Renal hypertension was induced according to the method of Grollman, 1944. Thereafter, the rats were given 0.9% sodium chloride daily for 6 weeks. Only rats with confirmed hypertension were further evaluated for the effect of the extract on their blood pressure. The results showed that the extract reduced the systolic, diastolic and mean arterial pressure and heart rate, dose dependently in both normotensive and hypertensive rats. This blood pressure lowering effect was not affected by 1mg/kg of atropine or promethazine. The study concluded that the fact that *N. latifolia* had blood pressure lowering effect seems to justify its use as antihypertensive agent by the traditional medicine practitioner. Further work is therefore, desired to ascertain the blood pressure lowering mechanism of this plant.

In another study, Odey *et al.*, (2012) investigated the antihypertensive properties of the root and stem of *N. latifolia*, by assessing the serum electrolytes levels in hypertensive animals treated with the ethyl alcohol extracts. The stem extract produced a significant decrease ($p<0.05$) of sodium in the treated animals compared to that of the hypertensive. The chloride levels in the treated and control groups were not significant ($p>0.05$), and the potassium levels were insignificant in the treated and control groups ($p>0.05$). Also, the potassium levels for the root extract treated animals were insignificantly lower ($p>0.05$) than the controls, while the sodium and chloride levels were significant ($p<0.05$). The reduced levels of these electrolytes, especially sodium showed that the *N. latifolia* extracts have antihypertensive properties.

8. Hypolipidemic Effect

The ethanol extract and its fractions were evaluated in this study to unravel their effects on the lipid profile of diabetic rats after daily administration for a period of two weeks (Edet *et al.*, 2013). The results showed that there were significant decreases ($p < 0.05$) in the HDL-cholesterol and total cholesterol levels in all the treatment groups. Insignificant decreases ($p > 0.05$) in TG levels were recorded in all the treatment groups whereas VLDL-C levels significantly decreased ($p < 0.05$) in the groups treated with glibenclamide, methanol fraction (100 mg/kg) as well as butanol and ethyl acetate fractions. Also, the n-hexane and ethyl acetate fractions as well as ethanol extract gave hope in arresting hyperlipidemia resulting from diabetes mellitus in diabetic rats.

Effect on cardiovascular system

Akpanabiatu *et al.,* (2005) examined the effect of *N. latifolia* leaf extract on lipid profile and cardiovascular activity of rats. The findings showed that ethanol extract of *N. latifolia* has vasodilator action on the aorta and that lipid profiles of experimental rats were not affected. Furthermore, the increase in the K+ may be contributing to the vasodilator effect of *N. latifolia*.

Hypocholesterolemic activity

Omale and Ugede, 2011 studied the cholesterol lowering effect of *N. latifolia* fruit as well as its toxicity and effect on hemoglobin, red and white blood cells count in albino rats. Experimental animals were fed the commercial feed supplemented at 40, 60 and 80% with *N. latifolia* fruit while the control group was fed the commercial rat feed alone daily for 28 days. The crude methanolic fruit sample lowered plasma cholesterol at 40, 60 and 80% feed supplementation studied in a dose dependent. There was also dose dependent increase in white blood cells at 40, 60 and 80% feed supplementation (4.23±0.01, 4.38±0.01, 4.40±0.03 (X109/L), respectively). Hemoglobin and red blood cell count decreased dose dependently. The LC_{50} of the plant extract was 1240.73 µg/ml conferring lower toxicity when compared with reference standard, potassium dichromate (LC50 = 176.86 mg/ml). The study suggested that *N. latifolia* possesses hypocholesterolemic potential (85.20±0.05 mg/dl when compared with control 136.25±0.005 mg/dl) and is relatively non-toxic (LC_{50}=1240.73µg/ml).

Hepatotoxic and Nephrotoxic Activity

Arise *et al.*, (2012) evaluated the effects of administration of aqueous extract of *N latifolia* stem on lipid profile and some liver and kidney parameters in rats. The results showed a significant concentration dependent decrease in total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C) and increase in low density lipoprotein cholesterol (LDL-C) and triglyceride (TG). Similar results were obtained in serum concentration of creatinine and urea with TC and HDL-C. There was also significant concentration dependent reduction ($P<0.05$) in liver and kidney alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase activities with a corresponding significant increase in their serum activities. The authors concluded that repeated administration of this extract may lead to damage in the kidney and liver.

Ogenyi *et al.,* 2015 also reported the histopathological and biochemical effects of ethanolic crude extracts of *N. latifolia* leaves, fruits, stem and root barks on the liver of Chinchilla rabbit. The results showed that rabbits treated with 250 mg/kg for 20 days, 40 days and 60 days showed significant elevation of AST and ALT activities. However, significant decrease in AST activity was observed when the animals treated for 40 days were compared with those treated for 60 days. There was no significant change in serum ALP in all the groups. Groups B and C treated for 60 days showed hepatic injury. The study suggested that crude ethanolic extract of *N. latifolia* fruits, leaf, stem bark, and root bark possessed the tendency to adversely affect hepatic functions.

Hepatoprotective activity

Yesufu *et al.*, (2010) studied the hepatoprotective properties of the aqueous root bark extract of *N. latifolia* by investigating its effect on some serum biochemical parameters in rats treated with Carbon tetrachloride (CCl_4).

The results showed that alanine transaminase (ALT), aspartate transaminase (AST), total and conjugated bilirubin levels were significantly decreased ($P<0.05$) across all the groups treated with extract and the toxin (CCl_4) in a dose dependent manner. It was concluded that the extract possess hepatoprotective properties. Future studies are needed to isolate the active ingredient and possible mechanism of action of the components of these extracts.

Edagha *et al.,* (2014) in another study, investigated the effect of ethanolic leaf extract of the plant on the hematological indices and histomorphology of the liver of male Swiss albino mice infected with Plasmodium berghei. The results revealed that the extract exhibited a significant hepatoprotective and reversibility effects at a dose dependent level on the histological architecture of treated groups compared with the control, and also caused a significant ($P < 0.001$) reduction in the RBC indices in a dose dependent manner especially in non-parasitized mice.

Hypoglycaemic activity

Gidado *et al.*, (2005) evaluated the hypoglycemic property of aqueous leaf extract of *N. latifolia* in normal and alloxan-induced diabetic rats. The aqueous extracts at (200 mg/kg b. wt.) significantly lowered glucose levels ($p<0.05$) of the diabetic rats by 45% within 4 h but showed no similar effect in normoglycaemic rats. The study suggested that aqueous extract of the leaves of *N. latifolia* possessed hypoglycaemic activity to warrant further detailed study to elucidate its therapeutic, toxicological and phytochemical properties.

In a similar study, Effiong *et al.,* (2013) evaluated the hypoglyceamic effect of ethanol extract and fractions of *N. latifolia* leaves in rats. The result in normoglycaemic rats showed maximum glycaemia reduction of 26.4% within 4 hours in the group treated with butanol fraction (250 mg/kg) which proved efficacious than glibenclamide at $p < 0.05$. Also, similar advantage over glibenclamide was recorded in ethanol extract (250 mg/kg) given alloxan-induced diabetic rats with % glycemic change of 44.4% as compared to 32.2% of glibenclamide within 4 hours n-hexane fraction (100 mg/kg) and butanol fraction (250/kg) recorded maxima % glycemic changes of 73.2% and 71.2%, respectively, within a period of 14 days at $p < 0.05$ in alloxan-induced diabetic rats. These findings suggest that ethanol extract and fractions of *N. latifolia* leaf possess hypoglycemic effects in animal model.

Gidado *et al.,* (2012) further studied the underlying mechanism of the hypoglycaemic activity of ethanolic extract *N. latifolia* in rats. The study concluded that the hypoglycaemic effect appeared to be probably exerted through a mechanism similar to that of glibenclamide which is related to increase insulin release from pancreatic β- cells.

Antidiabetic effect

Gidado *et al.,* 2009 studied the antidiabetic and possible toxicity effects of ethanolic leaf extract of *N. latifolia* in streptozotocin-induced diabetic rats. Extract doses of 100, 200 and 400mg/kg body weight were given orally to the STZ-induced diabetic rats daily for 45 days. The extract showed significant hypoglycaemic effect which was not dose dependent. Indices of liver and kidney functions studied were not statistically affected by the extract administration. Ethanolic leaf extract of *N. latifolia* thus exhibited antidiabetic action in STZ-induced diabetic rats with minimal toxicity.

Antia and Okon, 2014 also reported the antidiabetic activity of ethanolic root extract of *N. latifolia* in alloxan-induced diabetic rats after a single dose (acute study) and prolonged treatment (chronic study). The diabetic rats were treated with the root extract (150 – 450 mg/kg) and blood glucose level (BGL) was measured using a glucometer. Treatment of alloxan diabetic rats with the root extract (150 – 450 mg/kg, p.o) caused a significant ($P<0.05$ - 0.001) reduction in fasting Blood Glucose levels (BGL) of the diabetic rats both in acute study (7 h) and prolonged treatment (2 weeks) in a dose dependent manner comparable to that of the reference drug, glibenclamide (10 mg/kg b. wt., p.o). The study suggested that the root extract of *N. latifolia* posses antidiabetic effect on alloxan-induced diabetic rats which can be exploited in the management of diabetes.

Neuropharmacological effect

Amos *et al.*, (2005) evaluated the neuropharmacological effects of the aqueous root bark extract of *N. latifolia* in rodents. Effects on the spontaneous motor activity (SMA), exploratory behaviour, pentobarbital sleeping time, apomorphine-induced stereotypic behaviour and motor coordination (rota-rod performance) were investigated. The extract (50–200mg/kg, p.o.) significantly ($P<0.05$) decreased the SMA and exploratory behaviour in mice and prolonged pentobarbital sleeping time in rats dose-dependently. The extract also remarkably attenuated the intensity of apomorphine-induced stereotypy dose-dependently in mice, but had no effect on motor coordination as determined by the performance on rota-rod. The authors suggested that there is presence of psychoactive substances in the aqueous extract of the root bark of *N. latifolia* which are sedative in nature. Further studies to identify and isolate the active components are in progress.

Edagha *et al.*, (2015) examined the effect of ethanolic leaf extract of *N. latifolia* and *Emilia sonchifolia* on anxiety, fear and locomotion in mice infected with *Plasmodium berghei berghei* using open plus maze and elevated plus maze. The results obtained showed that grooming frequency and stretch attend frequency were significantly ($p<0.001$) lower in pre-treated groups compared with the control group. The combined extract treatment in group 5 was significantly ($p<0.001$) reduced compared with the parasitized non treated group. Line crossing duration was significantly ($p<0.001$) lower in groups 2 and 4 but significantly higher in groups 3 and 5 compared with the control group. This study concluded that both extracts were able to decrease fear and anxiety in parasitized mice while increasing their locomotion and exploratory activity.

Anticonvulsant, anxiolytic and sedative activity

Ngo Bum *et al.*, (2009) reported the anticonvulsant, anxiolytic and sedative activity of root bark of *N. latifolia* Smith (Rubiaceae) in mice. In the animal models studied, maximal electroshock-, pentylenetetrazol-, and strychnine-induced convulsions; N-methyl-D-aspartate-induced turning behaviour; elevated plus maze; stress-induced hyperthermia; open field; and diazepam-induced sleep were assessed. The decoction from the bark of the roots of *N. latifolia* strongly increased the total sleep time induced by diazepam. It also protected mice against maximal electroshock-, pentylenetetrazol-, and strychnine-induced seizures. In addition, turning behaviour induced by N-methyl-D-aspartate was inhibited. The extract antagonized, in a dose-dependent manner, stress-induced hyperthermia and reduced body temperature. In the elevated plus maze, N. latifolia increased the number of entries into, percentage of entries into, and percentage of time in open arms, and reduced rearing, head dipping, and percentage of time in closed arms. In the open field test, it increased crossing and reduced rearing and defecation. The authors concluded that the decoction of *N. latifolia*, used in traditional medicine in Cameroon for the treatment of fever, malaria, insomnia, anxiety and epilepsy seemed to possess, sedative, anticonvulsant, anxiolytic and antipyretic properties in mice.

Antidepressant, Myorelaxant, and Anti-anxiety-like activity

Ngo Bum *et al.*, (2010) reported the behavioural activity of the decoction of the roots of *N. latifolia* in rats. In this study, in vivo paradigms namely forced swimming test, horizontal wire test and hole-board test were used to detect antidepressant, myorelaxant and anti-anxiety properties in the animal models. The relationship between the neuropharmacological action of the extract and changes in GABA concentration in the brain were also examined. The extract was administered at a dose of 16, 40, 86, 160 and 360mg/kg orally 1 h before the test. The result showed that the extract induced a reduction of immobility in a similar way to that of fluoxetine, along with a significant increase in the percentage of spent time in swimming behaviour. The extract also displayed a myorelaxant activity in the horizontal wire test and significantly increased the number and duration of head-dips in the hole-board test. This finding suggests that the extract possess antidepressant, myorelaxant and anti-anxiety-like properties. The extract might potentially act by GABAergic activation and/or by modulating the serotonergic levels in the central nervous system. Further studies are needed to confirm this mechanism of action.

Anti-nociceptive, Anti-inflammatory, and Antipyretic effects

Abbah *et al.*, (2010) evaluated various concentrations of the aqueous extract of the root bark of *N. latifolia* for its anti-nociceptive, anti-inflammatory and anti-pyretic activities in mice and rats. Investigation of the anti-nociceptive activities was performed using the acetic acid-induced abdominal constriction and hot-plate tests in mice and formalin-induced pain test in rats, as models of nociception. The extract was also investigated for its effect against inflammation induced by egg-albumin and pyrexia induced by yeast in rats. The results showed that the extract (50–200 mg/kg p.o.) significantly ($P < 0.05$) attenuated writhing episodes induced by acetic acid and increased the threshold for pain perception in the hot-plate test in mice, dose-dependently. The extract also remarkably decreased both the acute and delayed phases of formalin-induced pain in rats and also caused a significant reduction in both yeast-induced pyrexia and egg-albumin-induced oedema in rats in a dose-dependent manner. The results suggest the presence of biologically active principles in the extract with anti-nociceptive, anti-inflammatory and anti-pyretic activities that justifies its use in malaria ethno pharmacy and subsequent development for clinical application.

In another study, Taiwe *et al.*, (2011) investigated the effects of N. latifolia roots decoction on the peripheral and central nervous systems and its possible mechanisms of action with respect to its analgesic and antipyretic effect. The analgesic investigation was carried out against acetic acid-induced writhing, formalin-induced pain, hot-plate and tail immersion tests. The antipyretic activity was studied in Brewer's yeast-induced pyrexia in mice. Rota-rod test and bicuculline-induced hyperactivity were used for the assessment of locomotors activity. The results obtained show that the extract induced hypothermia and had antipyretic effects in mice. It also produced significant antinociceptive activity in all analgesia animal models used. The antinociceptive effect exhibited by the decoction in the formalin test was reversed by the systemic administration of naloxone, N_{ω}-L-nitro-arginine methyl ester or glibenclamide. In contrast, theophylline did not reverse this effect. The extract (antinociceptive doses) did not exhibit significant effect on motor coordination of the mice in rota-rod performance but protected mice against bicuculline-induced behavioural excitation. These results demonstrate that the central and peripheral effects of N. latifolia roots decoction might partially or wholly be due to the stimulation of peripheric opoid receptors through the action of the nitric oxide-cyclic GMP-ATP-sensitive K^+ (NO/cGMP/ATP)-channel pathway and/or facilitation of the GABAergic transmission.

Taıwe *et al.*, (2014) further evaluated the antinociceptive effects of the alkaloid fraction isolated from *N. latifolia* in neuropathic pain induced by chronic constriction injury (CCI) of the sciatic nerve in rat. Bioactive-guided fractionation of the root extracts *of N. latifolia* using the Von Frey in a rat model of neuropathic pain (Bennett model), afforded a potent antihyperalgesic fraction IV. Further fractionation of this fraction was performed by high performance liquid chromatography (HPLC) and this yielded eight sub-fractions (F1–F8) which were tested for antinociceptive effects. The alkaloid fraction (F3) collected by HPLC, exhibited potent antinociceptive effects, and the anti-allodynic and anti-hyperalgesic effects of this fraction (8, 16, 40 and 80 mg/kg) were determined using the von Frey and acetone tests

respectively in a rat model of neuropathic pain. Rota-rod performance and catalepsy tests were used for the assessment of motor coordination.

The results showed that the alkaloid fraction (80 mg/kg) administered intraperitoneally induced a completely decreased hyperalgesia 90 min post-dosing. In the acetone test, the *N. latifolia* fraction at 80 mg/kg showed its maximal anti-allodynic effects 120 min post-injection. The areas under the curve (AUC) of the anti-allodynic or anti-hyperalgesic effects produced by the alkaloid fraction at 80 mg/kg were significantly ($p<0.001$) greater than the AUC of effects produced by vehicle in CCI rats. The alkaloid fraction did not exhibit any significant effects on the spontaneous locomotors activity of the mice in rota-rod performance and no sign of catalepsy was observed. This finding supports the traditional use of *N. latifolia* in neuropathic pain therapy. Further study is needed to characterize the mechanism(s) responsible for this anti-hyperalgesic and anti-allodynic action and also to identify the active substances present in the roots extracts of *N. latifolia*.

9. Biochemical Effects

Effiong and Akpan, (2015) investigated the effect of ethanolic leaf extract of *N. latifolia* on some biochemical parameters in streptozocin diabetic rat models. Groups 1 and 2 serving as non diabetic and diabetic controls received placebo treatment, groups 3 received 200mg/kg b. wt. the extract twice a day while the 4th group received subcutaneous insulin, 5IU/kg b. wt. per day, for 21 days. The results showed that blood glucose in diabetic animals decreased significantly from initial value by 61.51% upon treatment with the extract. Whereas diabetes induction caused significant increases ($p<0.05$) in total cholesterol by 54.42% and low density lipoprotein by 55.0% compared to the normal control (NC), treatment with extract of NL significantly decreased ($p<0.05$) these by 24.79% and 33.38% respectively. Also the amino transferases (ALT and AST) activities which increased by 66.83% and 72.87% in the diabetic control rats indicating hepatotoxicity secondary to hyperglycemia became reduced upon treatment with the extract. The study concluded that *N. latifolia* extract may provide a high efficacy in protection against atherosclerosis and hepatotoxicity in diabetes.

Effect on hematologic parameters

Asanga *et al.,* (2013) determined the effect of ethanol extract and fractions of *N. latifolium* leaves on the hematological property of alloxan-induced diabetic Wistar rats. N-hexane (100, 250 mg/kg), ethyl acetate (100, 250 mg/kg), butanol (100, 250 mg/kg) and methanol (100, 250 mg/kg) fractions of the ethanolic leaf extract of *N. latifolia* were orally administered once daily for 2 weeks to diabetic rats while the diabetic control groups received 30% Tween 80 and 5mg/kg of glibenclamide respectively. The levels of RBC, Hb, HCT, MCV, MCH, MCHC, PLT, PCT, MPV, PDW, WBC, lymphocyte and granulocyte were evaluated in blood. The result showed a significant reduction ($P < 0.05$) in RBC and HCT levels in the treatment groups of ethyl acetate fraction (250 mg/kg) and ethanol extract (250 mg/kg) with significant increases ($P < 0.05$) in their MCV and MCH levels when compared with the diabetic control group. Significant increases ($P < 0.05$) in PLT levels of the treatment groups of ethanol extracts, n-hexane fractions and ethyl acetate fraction (100 mg/kg); PCT levels of ethanol extracts group and MPV levels of ethyl acetate fractions treatment groups was high. The treatment groups of glibenclamide, butanol, methanol, n-hexane, ethyl acetate fractions and ethanol extract (250 mg/kg) showed significant reduction ($P < 0.05$) in their WBC and lymphocyte levels while significant increase ($P < 0.05$) in granulocyte levels was noted in the treatment group of ethanol extract (100 mg/kg) when compared with diabetic control group. The study concluded that the ethanol extract proved to have anti-infective property while some fractions showed capabilities to boost the immune system. They authors recommended further study on the ethyl acetate, butanol and methanol fractions to isolate and identify the components responsible for their hematoprotective property.

Wound healing effect

Udobre *et al.*, (2012) investigated the wound healing activity of methanol crude extract and the n-hexane, dichloromethane, ethyl acetate and butanol fractions of the stem bark of *N. latifolia* in rabbits. Wound was inflicted on animals by excising approximately 400mm^2 area of tissue from the back of the rabbit. In group 1 serving as negative control, wound dressing was done daily using distilled water. Group 11 received crude methanol extract dressing while groups 111, 1V, V, V1 received n-hexane, dichloromethane, ethyl acetate and butanol fraction solution dressing respectively. Wound contracture was assessed by tracing the wound area on a transparent graph paper from which wound surface area was evaluated on day 0, 4, 8, 12, 16, 20, 24 day. The % mean wound contraction area in day 24 were 57.88±0.17 (control), 63.04±0.14 (butanol), 63.88±0.05 (dichloromethane), 69.96±0.07(n-hexane), 74.00±0.08 (methanol) and 100.00± 0.00 (ethyl acetate). A better healing pattern with complete wound closure was observed in rabbits treated with ethyl acetate fraction within 24 days while it took 30 to 35 days in control rabbits. There was a significant increase ($p\leq0.05$) in wound contraction from day 4 onwards in all the treated rabbits except those treated with butanol fraction in day 4. This study provided a scientific rationale for the traditional topical application of the powdered stem bark of *N. latifolia* on wounds. Further studies are therefore needed to better assess the potential value of *N. latifolia* extracts as wound healing agents.

Effect on neonatal kidney

Histomorphological study of the effect of ethanolic leaf extract of *N. latifolia* on neonatal kidney was investigated in

rats (Solomon *et al.*, 2014). This study was divided into 3 phases, each phase consisting of 4 groups (one control group and three experimental groups). In all the 3 phases, the control groups (1A, 2A and 3A) received 10% Tween 80. In phase 1, the experimental animals designated (1B, 1C and 1D) received, 500mg/kg, 1000mg/kg and 1500mg/kg of *N. latifolia* respectively for 21 days before pregnancy. In phase 2, the experimental group animals designated (2B, 2C and 2D) received, 500mg/kg, 1000mg/kg and 1500mg/kg of *N. latifolia* respectively for 21 days before pregnancy and 7th to 13th day of gestation. In phase 3, the experimental group animals designated (3B, 3C and 3D) received 500mg/kg, 1000mg/kg and 1500mg/kg of *N. latifolia* respectively from 7th to 13th day of gestation and the litters were sacrificed within 48 hrs and tissues were processed using haematoxylin and eosin (H & E). The results showed that the extract affected the cytoarchitecture of the neonatal kidney in the experimental animal causing abnormal cellular pattern with areas of inflammation and necrosis in a dose dependent manner. This signifies the use of this plant during pregnancy imposes deleterious effect on neonatal kidney and the usage should be discouraged during pregnancy.

Effect on reproductive functions

Ikpeme *et al.,* (2013) investigated the possible adverse effects of stem bark ethanolic extracts of *Cylicodiscus gabunensis*, *N. latifolia* and *Araliopsis soyauxii* on male reproductive organs and sex hormones of male albino rats. Hormonal assay for total levels of testosterone, follicle stimulating hormone (FSH), luteinizing hormone (LH) and prolactin using the commercial kit, Microwell enzyme linked immunoassay (ELISA) technique was performed after treatment with these extracts. Sperm count, motility, viability, head abnormality, semen pH and weight of organs were also estimated. The results obtained on the reproductive organs showed no significant effect ($p>0.05$) on organ weight (testes and epididymidis), semen pH, sperm count and sperm head abnormality among the different groups but there were differences ($p<0.05$) in sperm motility and sperm viability in the different groups of the animal. On the hormonal analysis, the sex hormones under this study were generally decreased ($p<0.05$) as the concentration of each extract was increased. Thus, this study has x-rayed the potential reductive effects of the extracts of *C. gabunensis, N. latifolia and A. soyauxii* on sex hormones and some sperm parameters. They should be taken with caution as the administration of high dose could be fatal to sex hormones and some reproductive organs which might result in infertility.

Effect on ocular antioxidant system

Malaria has been shown to be associated with increased production of free radicals whose activities can be reduced by antioxidants. Mordi *et* al., (2014) therefore, investigated the antioxidant capacity of aqueous leaf extract of *N. latifolia* against *Plasmodium berghei* patho-biochemical changes in the ocular tissue in mice. Mice used in this study were inoculated intraperitoneally with 0.1ml parasitized blood suspension and parasitaemia was assessed by thin blood films stained with Geimsa stain. Aqueous leaf extract of *N. latifolia* was orally administered at different doses (200 mg/kg body weight and 300mg/kg bogy weight daily) to both normal and malaria infected mice for a period of 4 days. Ocular reduced glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), and Malondialdehyde (MDA) levels were estimated. The result showed significant ($p<0.05$) reduction in ocular reduced glutathione, decreased activities of ocular SOD and CAT, and increase in MDA levels in parasitized control when compared with normal control mice. However, the oral administration of *N. latifolia* significantly ($p<0.05$) increased ocular SOD, CAT activities with a significant decrease ($p<0.05$) in MDA content of parasitized mice. Non-enzymatic antioxidant (GSH) activity was also enhanced in a dose dependent manner of leaf extract administration. The outcome of this study indicates that malarial infection caused by *P. berghei* release free radical which could lead to oxidative stress in the ocular tissue as well as other part of the organism and that treatment with *N. latifolia* showed positive improvement in the antioxidant status.

Effect on non pregnant uterus

Nworgu *et al.,* 2010 investigated the anti-abortifacient effect of ethanolic extract of the root of *N. latifolia* via agonist-induced contractions of uterine smooth muscles in non-pregnant female albino rats. The extract, at 0.1 and 0.2 mg/ml (final bath concentration), was tested against oxytocin (4x10-5 to 8x10-2 I.U/ml: final bath concentration), acetylcholine (0.04 to 40 Âµg/ml: final bath concentration) and ergometrine (0.05 to 100 Âµg/ml: final bath concentration) induced contractions *in vitro*. The effect of the extract was compared to that of (0.004 Âµg/ml: final bath concentration) salbutamol and (0.004 Âµg/ml: final bath concentration) atropine. Both concentrations of the extract significantly shifted the concentration response curves of oxytocin ($P<0.01$), acetylcholine ($P<0.0001$) and ergometrine ($P<0.0001$) to the right with a slight depression of the Emax. This shift was more with the 0.2 mg/ml concentration, thus suggesting the possibility of a dose dependent action. There was no statistical significant decrease in Emax by 0.1 mg/ml of the extract, while the 0.2 mg/ml produced a significant depression ($P<0.05$) of the Emax, which like salbutamol could not be overwhelmed by higher concentrations of oxytocin. Similarly a significant reduction of the Emax of acetylcholine induced contractions was produced by 0.2 mg/ml, while both concentrations (0.1 and 0.2 mg/ml) produced significant ($P<0.0001$) reduction in Emax of ergometrine. The study concluded that *N latifolia* root extract non-competitively reduced oxytocin, acetylcholine and ergometrine-induced uterine contractions proving its anti-abortifacient property.

Table 5. Scientifically tested activities demonstrated by *Nauclea latifolia* extracts

ACTIVITY	REFERENCES
Antiulcerogenic	Balogun *et al*., 2013; Orole *et al*., 2013; Alaribe *et al*., 2014; Balogun *et al*., 2016.
Antisecretory	Balogun *et al.,* 2014; Balogun *et al*., 2015.
Antimicrobial	El-Mahmood *et al*., 2008; Okwori *et al*., 2008; Ahuocha, 2010; Ogueke *et al*., 2011; Maitera *et al*., 2011; Anowi *et al.,* 2012; Fadipe *et al*., 2013; Bamidele *et al*., 2014; Ifemeje *et al*., 2014.
Antiviral	Manuela *et al*., 2013; Onu *et al*., 2015.
Antihelmintic	Onyeyili *et al*., 2001; Ademola *et al*., 2007.
Antiplasmodial activity	Benoit-Vical *et al.,* 1998; Ettenbong *et al.,* 2015.
Antitrypanosomal	Maikai and Kobo, 2008.
Antioxidant	Ademola *et al*., 2014.
Antidiarrhoeal	Owolabi *et al*., 2010.
Antihypertensive	Nworgu *et al*., 2008; Odey *et al*., 2012.
Hypolipidemic	Akpanabiatu *et al.,* 2005; Edet *et al*., 2013.
Hypocholesterolemic	Omale and Ugbede, 2011.
Hepatotoxic and Nephrotoxic	Arise *et al*., 2012; Ogenyi *et al.,* 2015.
Hepatoprotective	Yesufu *et al*., 2010; Edagha *et al*., 2014.
Hypoglycaemic	Gidado *et al*., 2005; Gidado *et* al., 2012; Effiong *et al*., 2013.
Antidiabetic	Gidado *et al.,* 2009; Antia and Okon, 2014.
Neuropharmaologic	Amos *et al*., 2005; Edagha *et al*., 2015.
Anticonvulsant, Anxiolytic and sedative	Ngo Bum *et al*., 2009.
Antidepressant, Myorelaxantand Antianxiety-like	Taiwe *et al*., 2010.
Antinociceptive, Antiinflammatory and Antipyretic	Abbah *et al*., 2010; Taiwe *et al*., 2011; Taiwe *et al*., 2014.
Biochemical	Effiong and Akpan, 2015.
Hematologic	Asanga *et al*., 2013.
Wound healing	Udobre *et al*., 2012.
Neonatal kidney	Solomon *et al*., 2014.
Reproductive function	Ikpeme *et al*., 2013.
Ocular antioxidant system	Mordi *et al*., 2014.
Anti-abortifacient	Nworgu *et al.,* 2010.

Toxicity studies

Table 6

Subject	Extract	Mode	LD_{50} (mg/kg b. wt)	Remark	References
Mice	Ethanolic (100-1600mg/kg/day)	IP	1549.19mg/kg	Extract at dose of 100-2000mg/kg produced physical signs of toxicity-writhing, gasping, palpitation, decrease respiratory rate and death within 24 hrs. All mice treated with 1600mg/kg and above died.	Antia and Okon, 2014.
Rats	Ethanolic extract (500mg/kg b. wt.) 500mg-2000mg/kg 12hly @ 0,12 & 24hr	IP Orally		Structural changes were observed in the liver and kidneys following extract administration showing pathological lesion. Increase in marker enzymes and histopathological evidence.	Magili *et al.,* 2014.
Rats Mice	Aqueous extract of stem bark Acute toxicity- 2, 4, 8 & 18g/kg for 28days Sub acute toxicity-1.8, 18, 180mg/kg for 28days	Oral daily	18g/kg	Increase in platelet, erythrocyte & eosinophil count. Low serum concentration of ALT, AST & creatinine noted at 18 and 180mg/kg. Urine showed depletion of sodium and potassium with high loss of water. No structural changes noted. Low dose led to weight gain. May exert allergenic and inflammatory property. Safe relatively	Kouadio *et al.,* 2014.
Rat	Ethanol 30.2mg/kg, 60.4mg/kg, 120.8mg/kg, 241.6 mg/kg daily for 14 days.	IP		Decrease in RBC, PCV with increasing doses. Increase in WBC, ESR with increasing doses. At lower doses, does not affect erythrocytes.	Ogueke *et al.,* 2011.

10. Conclusions

N. latifolia smith has been used traditionally in the treatment of different ailments. Several researches carried out for years till now have shown pharmacologic potentials of this plant. However, further research is needed to elucidate the active ingredients and mechanism of action behind these proven pharmacologic activities.

11. Future Research Direction

- Isolation and screening of the active ingredients responsible for these pharmacologic activities.
- Elucidation of mechanism of action behind these proven pharmacologic activities.
- Clinical study
- Drug formulation

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