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Medicinal uses, pharmacological activities, and bioactive compounds of *Nauclea latifolia* and implications in the treatment of tropical diseases

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Abstract

Nauclea latifolia Sm. is a medicinal plant from the family Rubiaceae which is widely distributed in the tropical regions of Africa and Asia. Different parts of the plant are known to have many ethnomedicinal uses. The aim of this review is to compile knowledge available on the ethnomedicinal uses, pharmacological activities, and bioactive compounds present in different parts of the plant and identify their relevance in the treatment of tropical diseases. This review will preserve traditional knowledge, promote responsible use, and advance scientific and medical research on this plant. *N. latifolia* is used for the treatment of malaria, skin conditions, pain, hypertension, diabetes, fever, stomach problems, female infertility, gastric ulcer, jaundice, respiratory tract ailments, eye conditions, menstrual disorders, yellow fever, gonorrhoea, haemorrhoids, urine retention, male sexual dysfunction, dysentery, diarrhoea, HIV/ AIDS, measles, typhoid fever, leprosy, oral diseases, hernia, cancer, filariasis (helminthiasis) and central nervous system injuries. This plant has been investigated for its antidepressant, anticonvulsant, antimicrobial, antiplasmodial, antioxidant, antidiabetic, anti-ulcer, antipyretic, antinociceptive, hepatoprotective, larvicidal, ovicidal, antidiarrheal, antihypertensive, hypocholesterolemic, hypoglycaemic, anti-inflammatory, anxiolytic, myorelaxant and sedative activities. Scientific justification for its usage in the treatment of viral infections, hypertension, helminthiasis, stomachache, diabetes, backache, fever, cancer, malaria, diarrhoea, measles, conjunctivitis, and gastric ulcer has been established. However, further studies are needed to justify its use in the treatment of urine retention, male sexual dysfunction, HIV/ AIDS, hernia, female infertility, as well as Parkinson's and Alzheimer's disease. The phytoconstituents documented include proanthocyanins, alkaloids, tannins, flavonoids, glycosides, phenols, steroids, saponins, and terpenoids, with many compounds having been isolated.

Keywords: Nauclea latifolia, ethnomedicinal uses, phytochemistry, bioactive compounds, pharmacological properties, traditional uses

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INTRODUCTION

In Africa, medicinal plants have been used therapeutically since ancient times by early empirical observations and generational transmission via oral tradition. [Sofowora, A. (1996). Research on Medicinal Plants and Traditional Medicine in Africa. The Journal of Alternative and Complementary Medicine, 2(3), 365–372. doi:10.1089/acm.1996.2.365] are extensively used due to their long history of use in the African culture, but also in certain remote areas, even more appreciated due to limited access to modern healthcare services or as an augmentation to modern healthcare [1]. The use of medicinal plants is believed to be a fundamental component of the African traditional healthcare system and is perhaps the oldest and the most assorted of all the therapeutic systems [2]. The World Health Organization reports that 70% to 95% of the human population in most developing countries, including Africa, use medicinal plants for daily health improvement [3]. Africa is a tropical continent plagued with tropical diseases. The term tropical disease refers to a number of

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infectious diseases that commonly occur in the tropics due to the warm and moist environmental conditions, and these are often quite challenging to manage and control. These diseases include leishmaniasis, schistosomiasis, onchocerciasis, lymphatic filariasis, Chagas disease, African trypanosomiasis, dengue fever, and even malaria, diarrhoeal diseases and tuberculosis etc. [4]. Currently, the World Health Organization (WHO) recognizes 17 neglected tropical diseases (NTDs): Buruli ulcer, Chagas disease, cysticercosis, dengue fever, dracunculiasis, echinococcosis, endemic treponematoses, foodborne trematode infections, human African trypanosomiasis, leishmaniasis, leprosy, lymphatic filariasis, onchocerciasis, rabies, schistosomiasis, soil-transmitted helminthiases, and trachoma [5].

The treatment of neglected tropical diseases, in particular, has been challenging, resulting in millions of blind, maimed and disfigured individuals in the poorest parts of the world [5]. Medicinal plants have long been used in the management and treatment of various NTDs [6]. Most of these treatments are part of the traditional and alternative medicine systems, and some have gained recognition for their potential efficacy even in modern medical research, as is the case of the treatment of malaria with *Artemisia annua* [7]. In this respect, we review information available on *N. latifolia* Sm. from the family Rubiaceae. This is a medicinal plant widely used in West Africa for the treatment of several diseases [8]. *N. latifolia* is traditionally important in Ghana and Sub-Saharan Africa for both medicinal and non-medical purposes [8,9].

In Ghana, the plant is used non-medically as a roofing material and for firewood, while the fruits are consumed by some as food. The leaves, stem, and bark of *N. latifolia* are prepared as decoction in water and used traditionally against malaria [10] and other infections [11-14]. Also, decoctions of roots, bark, stem or leaves of the plant are taken as dewormers [15] and used for treating toothache, dental caries, septic mouth, diarrhoea and dysentery [16]. The citizens of Mali and Cote d'Ivoire use the aqueous extracts of *N. latifolia* to treat fever and malaria [17]. In addition to the numerous benefits of the plant to humans, it is also reported for use in the treatment of diseases that affect animals, such as diarrhoea [18-20] and helminthiasis [21]. Recently, researchers have developed an interest in the isolation of compounds present in different parts of *N. latifolia* in order to determine their bioactivity and toxicity. The investigation was occasioned following the isolation of the synthetic analgesic tramadol at a considerable at a considerable concentration from the root bark [22]. Such findings are rare in nature. The medicinal potentials of *N. latifolia* necessitate this review of its ethnomedicinal uses, pharmacological activities, and bioactive compounds.

MATERIALS AND METHODS

Study design and sites

From November 2020 to July 2021, relevant articles were accessed from Google Scholar, Science Direct, Web of Science, and African Journals Online. Key terms that were used in the search included phytochemistry, bioactive compounds, pharmacological properties, pharmacological activity, pharmacological model, *Nauclea latifolia*, *Sarcocephalus latifolius*, African Peach, Pin Cushion tree, traditional uses, ethnomedicinal uses, herbal medicine, indigenous, preparation and route of administration. The publications obtained were first screened using their abstracts, and subsequently, their full texts were reviewed. A total of 137 articles, books and book chapters were accessed. Information on the various ethnomedicinal uses, pharmacological activities, and bioactive compounds obtained from the literature sources is examined below.

RESULTS

N. latifolia belongs to the family Rubiaceae. The family Rubiaceae has about 611 Genera, with 13,100 species in the Wet Tropics [23]. The genus Nauclea has various species. *N. latifolia, N. diderrichii (De Wild. & Th.Dur.) Merrill, N. gilleti (De Wild.) Merr, N. vanderguchtii (De Wild) Petit, N. pobeguinii (Pobég. ex Pellegr.) Merr. ex E.M.A. Petit and N. xanthoxylon* (A.Chev.) Aubrév. are those commonly found in Africa [24]. N. latifolia is known in English as an

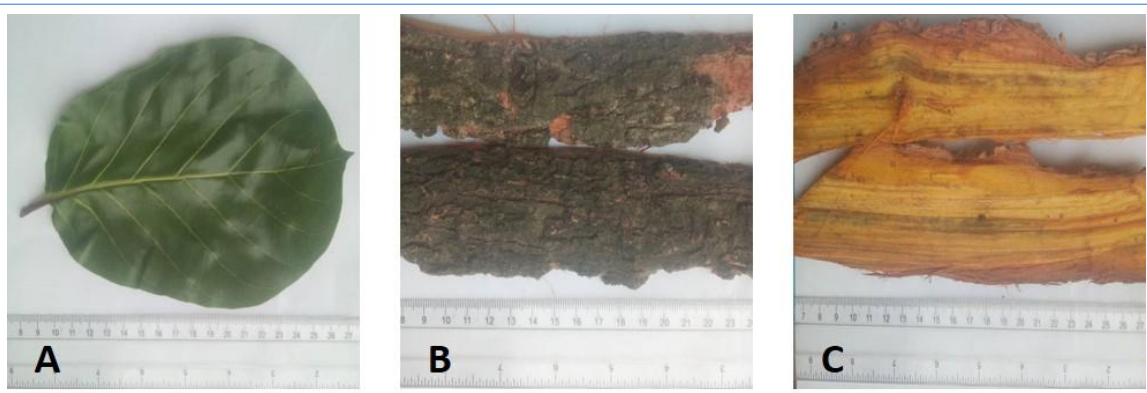

Figure 1. Leaf (A), Outer bark (B), Inner bark (C) of N. *latifolia*

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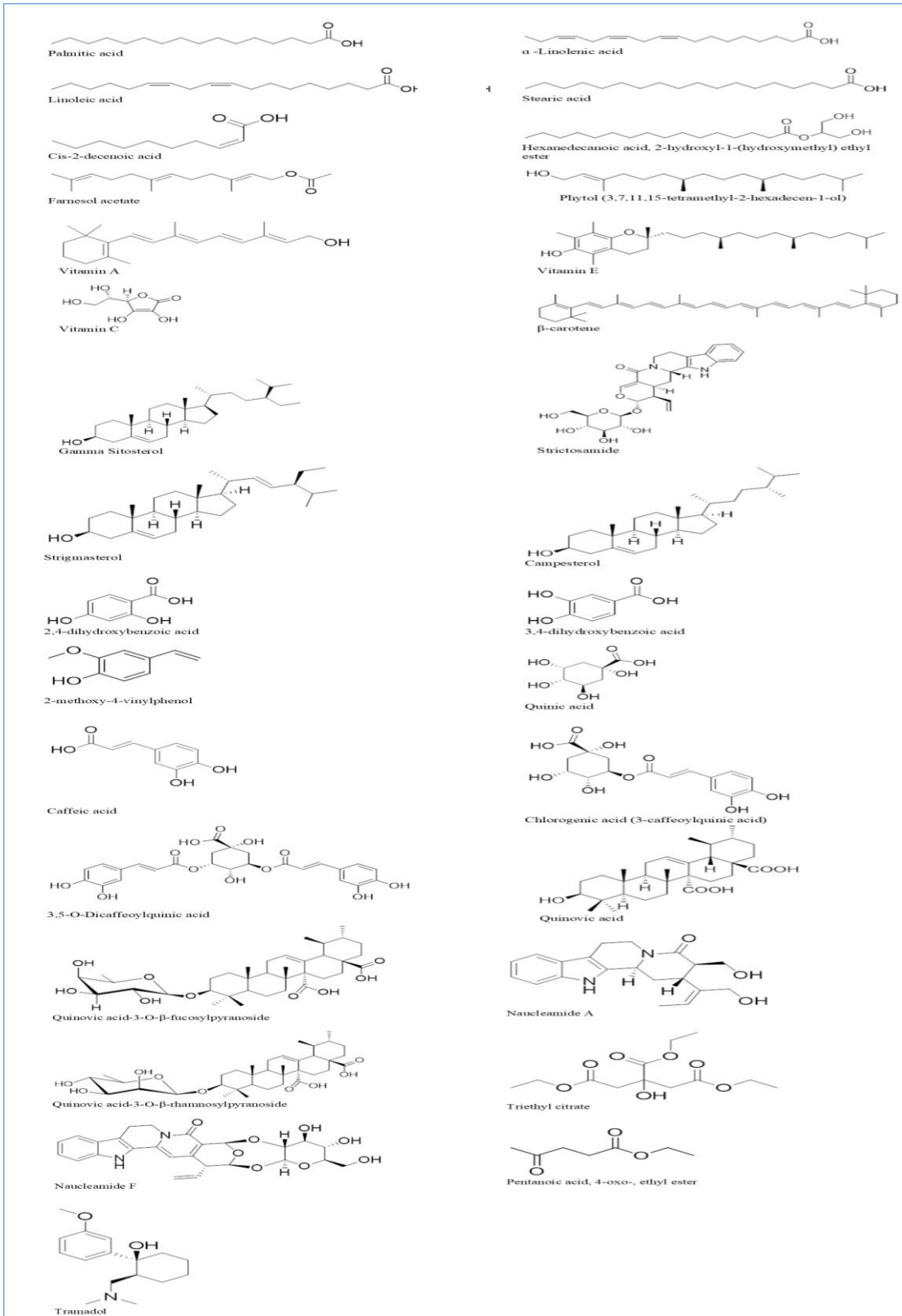

Figure 2. Bioactive molecules of N. latifolia

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Table 1. Treatment of Malaria using *N. latifolia*

Plant Part	Preparation	Administration	Country/ Region	Reference
Roots	Decoction	Oral	Benin/ Plateau of Allada	[34]
Roots, Leaves	Decoction (Root) Maceration (Leaves)	*N/A*	Burkina Faso/ Baskoure, Kourritenga Province	[31]
Stem bark, Roots	Decoction	Oral	Cameroon / Yaoundé and Mbalmayo	56
Stem	Maceration	Oral	Ghana/ Eastern, Central, Greater Accra and Ashanti regions	[42]
Roots Root bark	Decoction Infusion	Oral	Ghana/ Dangme West District/ Northern	[10, 41]
Leaves, Roots, Stem bark, Root bark	Decoction	Oral, Steam bath	Guinea/ All regions	[55], [54]
Leaves, Bark	Maceration (Bark) Decoction (Leaves)	Oral	Mali/ All regions	[14]
Leaves	Decoction	Oral, Bath	Mali/ Sélingué subdistrict	[53]
Bark, Roots	Decoction (Root)	Co-administered orally with other plant species.	Nigeria/ Ogun state	[49]
Bark, Roots	Decoction (Root)	Co-administered orally with other plant species.	Nigeria/ Ogun state	[49]
Leaves Co-administered orally with other plant species	Decoction	Oral	Nigeria/ Ogun state/ Okigwe Imo state	[45, 47]
Leaves	Infusion	Oral	Nigeria/ Ekiti state	[44]
Leaves, Roots, Stem bark	Maceration (Leaves)	Co-administered orally with other plant species	Nigeria/ Southern region	[48]
Leaves	Decoction	Oral	Nigeria/ South West	[133]
Leaves, Stem bark, Roots	Tincture (Root), Decoction (Root)	*N/A*	Nigeria/ Southern	[134]
Stem, Roots	Decoction	Oral	Ghana	[135]
Roots	Maceration, Decoction, Infusion	Oral	Nigeria/ Akwa Ibom state	[136]
Leaves	Maceration	Co-administered orally with other plant species	Sierra Leone	[57], [56]
Roots	Decoction, Maceration	Oral	Togo/ Plateau and Maritime region	[50], [51]
Stem, Bark	Aqueous infusion	Oral	Ghana/ Accra	[9]
Roots, Leaves	Maceration (Root)	Oral	Togo	[52]

Table 2. Treatment of Skin Conditions using *N. latifolia*

Disease	Plant Part	Preparation	Administration	Country/ Region	Reference
Boils	Roots	Decoction	Oral	Nigeria / Rivers state	[59]
Itching	Roots, Stem	Decoction	Bath	Nigeria / Benue and Ekiti states	[30], [60]
Burns	Leaves	Infusion	Bath	Senegal / Kédougou	[65]
Wounds and Infantile dermatosis	Inner bark, Stem, Sap, Fruit, Roots, Root bark	Decoction	Oral	Nigeria / Odeda and Lagos state	[63], [62]

Table 3. Treatment of Pain using *N. latifolia*

Disease	Plant Part	Preparation	Administration	Country/ Region	Reference
Backache	Roots, Leaves	Decoction (Root, Leaves)	Oral	Nigeria / Kainji Lake National Park	[66]
Headache	Leaves	Decoction	Oral, Bath	Mali/ All regions	[14]
Abdominal ache	Leaves, Roots	Infusion (Roots)	*N/A*	Senegal/ Kédougou	[65]
	Leaves, Roots, Bark	Decoction	Oral	Nigeria/ Abia and Bauchi State	[83], [35]
	Bark, Roots	Decoction (Bark, Roots), Maceration (Bark, Roots)	Oral	Mali/ All regions	[14]
	Roots, Leaves	Decoction	Oral	Burkina Faso/ Baskoure, Kourittenga Province	[31], [137]

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Table 4. Summary of Pharmacological Activities of *N. latifolia* Crude Extracts

Activity Tested	Plant Part	Extract	Methodology	Effect	Reference
Anticonvulsant	Root bark	Aqueous	Fisher's Exact Test	Extract at 160 mg/kg dose provided 75% and 71% protection of mice ($p < 0.01$) against strychnine-induced seizures and pentylenetetrazol-induced seizures, respectively.	[91]
Antidepressant	Root bark	Aqueous	Forced Swimming Test	Extract significantly shortened immobility time of mice.	[92]
Antidiarrheal	Root bark	Ethanol	Inhibition of Castor Oil- Induced Diarrhea	Extract showed a 77.42% protection against diarrhea.	[93]
			Small Intestinal Motility Model	Extract produced 50% dec rease in the propulsive movement of the charcoal meal through the small intestine.	
			Isolated Rat Ileum Model	Extract caused a significant dose-dependent relaxation on the acetylcholine-induced contraction.	
Antihypertensive	Root bark, Stem bark	Ethanol	Change in Body and Organ Weight in Wistar Rats.	Extract significantly reduced the body, heart, kidney, and liver weights.	[94]
	Roots	Ethanol	Change in Systolic Blood Pressure in Rats.	Extract at dose of 2.5 – 20 mg/kg and 2.5 – 10 mg/kg effectively lowered blood pressure in normotensive rats and in hypertensive rats, respectively.	[138]
Anti-inflammatory	Root bark	Aqueous	Egg-Albumin-Induced Inflammation in Rats.	Extract significantly reduced inflammatory responses in test rats.	[95]
Antimicrobial	Leaf	Ethanol	Agar Plate Method	Extract exhibited significant inhibitory activity against moulds, *Staphylococcus spp* and *Candida albicans.*	[98]
		Methanol		Extract exhibited significant inhibitory activity on *Candida albicans*, *Aspergillus spp* and moulds.	
	Stem bark	Chloroform	Agar Diffusion Method	Extract demonstrated activity against *E. coli, S. aereus, S. dysentariae, B. subtilis, C. albicans* and *P. aeruginosa* with percentage susceptibility of 64%, 64%, 82%, 64%, 58% and 70%, respectively.	[29]
	Root	N-hexane, Ethyl acetate, Methanol	Agar Diffusion Method	All three isolated compounds exhibited potent activity against eleven human pathogenic bacteria and fungi in the order 3,4 - dihydroxybenzoic acid > quinovic acid > strictosamide. The most susceptible were *E. aerogenes, P. vulgaris, S. aureus and C. albicans.*	[103]
	Stem bark, Leaves, Roots	Methanol	Agar Diffusion Method	Extracts actively inhibited *S.* dysenteriae, *E. coli, S. aureus* and *S. pneumonia* with zones of inhibitions of 10 -25 mm.	[74]
	Leaf	Methanol	Agar-Well-Diffusion Method	Extract exhibited activity against *S. typhi, S. enterica, E. coli* and *lactobacillus spp* with MIC of 0.782 mg/*mL*, 3.125 mg/*mL*, 1.563 mg/*mL*, and 1.563 mg/*mL*, respectively.	[100]
	Stem bark			Extract exhibited activity against *S. typhi*, *E. coli* and *lactobacillus spp* with MIC of 1.56 mg/mL, and against *S. enterica* with MIC of 3.125 mg/mL.	
	Leaves, Bark, Roots.	Aqueous	Agar-Well-Diffusion Method, Broth Dilution Method	All extracts exhibited activity against *K. pneumoniae, E. coli, P. aeruginosa, S. aureus* and *S. dysenteriae.*	[101]
		Ethanol		Ethanol extract exhibited higher activity against all the above micro- organisms as compared to the aqueous extracts.	
	Stem bark	Chloroform	Agar-Well-Diffusion Method	Extract was active against *S. aureus, B. subtilis, S. viridans, E. coli, K. pneumonia* and *A. niger* with MICs of 2.5, 10, 5, 5, 5 and 15 mg/*mL*, respectively.	[96]
		Methanol		Extract demonstrated activity against only *P. aeruginosa and S. aureus* with MICs of 20 mg/*mL* and 10 mg/*mL*, respectively.	
	Leaves	Methanol	Agar Cup- Plate Method	*B. subtilis, Cl. sporogens E. coli, K. pneumonia, P. fluorescence, P. aeruginosa, S. aureus* were susceptible to five isolated compounds: caffeic acid, quercitin, quercetin-3-O-*β*-glycopyranoside, chlorogenic acid and 3,5-O-dicaffeoylquinic acid with MIC ranges of 0.625- 5 mg/*mL*, 0.156- 2.5 mg/*mL*, 1 mg/*mL*, 1-10 mg/*mL* and 1.25- 5 mg/*mL* respectively.	[97]

Table 4. cont.

Activity Tested	Plant Part	Extract	Methodology	Effect	Reference
	Root bark	Dichloromethane-methanol mixture	Plaque and Viral Yield Reduction Assays	Extract, with an IC_{50} value of 1.46 µg/*mL* (95% CI:1.07 - 1.91), reduced the yield of the acyclovir-sensitive *Herpes simplex* virus-2.	[102]
	Leaves	Ethanol (hot)	Agar-Well-Diffusion Method	Extract exhibited activity against *E. coli, S. aureus and P. aeruginosa* with MICs of 3.24, 3.28 and 4.82 mg/*mL*, respectively.	[99]
	Stem bark	Ethanol	Agar-Well-Diffusion Method	Extract demonstrated activity against *S. aureus, E. coli, S. typhi* and *B. subtilis* with MIC of 2.5 mg/*mL*.	[104]
Antioxidant	Leaves	Ethanol	2,2- Diphenyl-1-Picrylhydrazyl (DPPH) Radical Scavenging Assay, Ferric Reducing Antioxidant Power (FRAP) Assay, Total Antioxidant Capacity (TAC) Assay	Extract showed significant activity against DPPH with an IC_{50} of 2.58±0.08 mg/*mL*, dose-dependent increase in FRAP with the highest power being 1314.45±197.64 mg AAE/g, and a dose- dependent increase in TAC with the highest capacity being 73.81± 2.27 mg AAE/g.	[105]
	Leaves	Methanol	DPPH Radical Scavenging Assay, FRAP Assay, TAC Assay, Nitric Oxide Inhibition Assay, Metal Chelating Ability (MCA) Assay	The isolated compounds (caffeic acid, quercetin, quercetin-3-O- *β*-glycopyranoside, chlorogenic acid and 3,5-O-dicaffeoylquinic acid) exhibited significant DPPH scavenging ability with IC_{50} range of 2.71 ± 0.09 to 21.3 ± 1.01 *µg/mL*. The isolated compounds) had good FRAP values ranging from 0.28 ± 0.01 to 1.21 ± 0.05 mg AAE/g. Also, all the isolated compounds demonstrated good TAC ranging from 2.57 ± 0.01 to 4.23 ± 0.23 mg AAE/g, and exhibited better inhibition of NO radical activities (IC_{50} ranged from 5.17 ± 2.59 to 55.17 ± 0.66 µg/mL). All the isolated compounds exhibited good MCA with the IC_{50} ranging from 104.55 ± 2.73 to 229.18 ± 7.76 *µg/mL*.	[97]
	Leaves, Fruits	Aqueous	DPPH Radical Scavenging Assay, FRAP Assay, Trolox Equivalence Antioxidant Capacity (TEAC), Oxygen Radical Absorbance Capacity (ORAC)	Leaf extract demonstrated better DPPH activity than fruit extract with IC_{50} values of 20.64 mg/*mL* and 120.33 mg/*mL* respectively, and showed higher FRAP (86.10 ± 3.46 *µ*mol AAE/g sample) than fruit extract (12.23 ± 0.40 *µ*mol AAE/g sample). Also, higher TEAC was demonstrated by the leaves extract than the fruits extract with values of 94.83 ± 3.57 *µ*mol TE/g sample and 12.48±0.21 *µ*mol TE/g sample, respectively, and the mean value of ORAC for leaves extract was 196.55 ± 0.073 *µ*mol TE/g sample while that of the fruits extract was 55.88 ± 0.073 *µ*mol TE/g sample.	[106]
	Root	Aqueous	Lipid Peroxidation and Oxidative Stress.	Extract reduced the activity of catalase, superoxide dismutase (SOD) and malondialdehyde (MDA) and restored the level of glutathione (GSH).	[107]
Antiplasmodial	Leaves	Aqueous	Curative Test	Extract caused significant decrease in organism parasitaemia in mice when compared to the negative control group.	[113]
	Leaves	Aqueous	Antioxidant Enzyme and Histopathological Changes	Extract eliminated *P. berghei* in the brain and liver tissues and improved antioxidant defense by restoring the levels of superoxide dismutase, catalase, and glutathione.	[114]
	Leaves	Aqueous	*In-Vitro* and *In-Vivo* Inhibitory Effect on haemozoin concentration	Extract exerted appreciable decrease on the haemozoin concentration at 24-hour intervals.	[111]
	Leaves	Methanol	Rane's Test	Extract caused a statistically significant dose-dependent decrease in organism parasitaemia, and a dose-dependent increase in the chemosuppressive effect on parasitaemia.	[110]

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Table 4. cont.

Activity Tested	Plant Part	Extract	Methodology	Effect	Reference
	Stem bark	Methanol	Rane's Test	Extract caused a dose-dependent reduction in parasitaemia.	[109]
		Ethanol		The groups treated with extract showed a significant dose-dependent decrease in parasitaemia.	[112]
	Roots	Ethanol	Suppressive and Curative Tests in Albino Mice	Extract at 150 mg/ kg caused 96.2% and 33.3% growth inhibition of *P. berghi* in suppressive and curative tests, respectively.	[108]
Antipyretic and Antinocicep tic	Root	Aqueous	Antipyretic Test	Extract caused a significant and dose- dependent hypothermia. Fever was reduced by 0.5 degrees Celsius one hour after administering 160mg/kg of extract.	[115], [95]
			Acetic Acid- Induced Abdominal Constriction	Extract caused inhibition of acetic acid- induced abdominal constriction in a dose- dependent manner.	
			Formalin- Induced Nociception	Extract caused a significant and dose-dependent inhibition of formalin-induced biphasic pain responses in mice.	
			Hot Plate Model	Extract produced a dose- dependent protection against heat- induced pain.	
			Tail Immersion Model	Extract produced a dose- dependent increase in tail withdrawal latency.	
		Ethyl acetate, n- butanol	Von Frey Test	The alkaloids fraction demonstrated dose- dependent inhibition of hyperalgesia with an ED_{50} value of 35.94 (24.25–51.39) mg/kg.	[116]
Anti- ulcer	Leaves	Aqueous	Gastro Mucosal Protection	Extract caused significant and dose- dependent anti-ulcer activity against indomethacin-induced ulcers in the rats-highest dose of 510 mg/kg produced 90.57% protection.	[77]
		Methanol		Extract at a dosage of 150 mg/kg body weight produced an ulcer index of one (1) in aspirin- induced rats and caused a reduction in free acidity, pH, and total acidity content.	[117]
	Stem bark	Aqueous	Gastric Mucus Production	Extract caused a significant and dose dependent elevation in gastric mucous production. At 200 mg/kg, extract produced curative ratios of 73.63% and 77.62% in ethanolic acid and indomethacin-induced ulcers, respectively.	[118]
	Stem bark	50% Methanol	Cytoprotective Assay	Extract significantly inhibited gastric lesions in aspirin and histamine-induced ulcer in rats.	[78]
			Cyto- Healing Assay	Extract dose of 100 mg/kg caused 60.35% healing in ulcerated gastric mucosal cell walls.	
			Anti-*Helicobacter Pylori* Assay	Extract demonstrated activity against *helicobacter pylori* with an MIC of 25 mg/*mL*.	
Anxiolytic	Root bark	Aqueous	Hole- Board Test	Extract reduced anxiety resulting in significant and dose- dependent increase in the number and duration of head- dips.	[92]
			Elevated Plus Maze Test	Extract reduced anxiety resulting in decreased percentage of time spent in closed arms, increased number of entries into, percentage of entries into, and time spent in open arms.	[91]
Hepatoprot ective	Root	Methanol	Biochemical and Histopathological Changes in Wistar Rats	Extract reduced serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels and attenuated deleterious histopathologic changes in liver caused by paracetamol and CCl_4.	[119]
	Root bark	Aqueous	Change in Serum Biochemical Markers	Extract at 300 mg/kg caused 44.3%, 8.1%, 37% and 47. 6% protection for aspartate transaminase, alanine transferase, total bilirubin, and conjugated bilirubin respectively in CCl_4 induced hepatotoxicity in rats.	[120]
Hypocholes terolemic	Leaves	Ethanol	Lipid Profile Analysis	Extracts caused reduction in the levels of triglycerides (TG), low density lipoproteins (LDL), very low-density lipoproteins (VLDL) and total cholesterol in alloxan- induced diabetic rats.	[125]
	Fruit	Methanol	Lipid Profile Change	Extract reduced plasma cholesterol in a dose-dependent order in albino rats.	[124]

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Table 4. cont.

Activity Tested	Plant Part	Extract	Methodology	Effect	
				Extracts caused a dose- dependent decrease in the levels of triglycerides (TG), low density lipoproteins (LDL) and very low-density lipoproteins (VLDL) in alloxan-induced rats.	[123]
Hypoglycaemic	Root	Ethanol	Body Weight and Blood Glucose Level	Extract caused a dose-dependent decrease in blood glucose level and a significant weight gain in alloxan-induced diabetic rats.	[128]
	Leaves	Aqueous	Blood Glucose Level	Extract lowered the blood glucose level in alloxan-induced rats by 79.9% after administration for three days.	[127]
				Extract lowered the blood glucose level in alloxan-induced rats by 45% four hours after administration.	[27]
	Leaves	Ethanol	Glucose Tolerance Test	Extract at dose 200 mg/kg significantly inhibited the increase in glucose level in Wistar rats after glucose load.	[129]
			Blood Glucose Level	Extract at 200 mg/kg dose lowered blood glucose level by 60.77% in streptozotocin-induced diabetic rats after 45 days of administration.	[126]
Larvicidal	Stem bark	Aqueous, Ethanol	Larval Mortality of *Heligmosomoides bakeri*	Extracts destroyed *H. bakeri* with median lethal dose (LC_{50}) of 243, 2246 and 713 µg/*mL* for hot, cold water and ethanolic extracts, respectively.	[122]
		Methylene Chloride: Methanol (1:1)	Larval Mortality of *H. Bakeri*	Extract at concentration of 5000 µg/*mL* caused 54.76% and 51. 44% mortality rates in the first and second larval stages respectively, 24 hours after administration.	[121]
	Leaves	Aqueous, Ethanol	Larval Development Assay	Extracts exhibited activity with median lethal dose (LC_{50}) of 0.704 mg/*mL* and 0.650 mg/*mL* for aqueous and ethanolic extract respectively with a statistically significant difference.	[32]
Myorelaxant	Root bark	Aqueous	Horizontal Wire Test	Extract produced a dose- dependent increase in the number of impaired mice. These impaired mice experienced significant muscle relaxation at concentration of 80 mg/kg, similar to that induced by diazepam.	[92]
Ovicidal	Stem bark	Aqueous, Ethanol	Egg Assays of *H. Bakeri*	Extracts exhibited activity with median Inhibitory Concentration (IC_{50}) of 1082, 4554 and 0.10 µg/*m* for hot, cold and ethanolic extract respectively.	[122]
	Stem bark	Methylene Chloride: Methanol (1:1)	Egg Assays of *H. Bakeri*	Extract inhibited embryonation in a dose-dependent manner. At maximal concentration of 5000 µg/*mL*, there was 38.15% inhibition of embryonation.	[121]
	Leaves	Aqueous, Ethanol	Nematode Egg Recovery Technique	Extract caused a reduction in the nematode egg count.	[32]
Sedative	Root bark	Aqueous	Diazepam-Induced Sleep Model	Extract at dose of 80 mg/kg increased the sleep time from 12 minutes in control group to 64 minutes in test group.	[91]

African peach or Pin cushion tree [25]. In Ghana, it is commonly called "kusia" among most Akans, "oyefa-owenfa" among the Gas, "nyimo" among the Ewes, and hwene hwenti" among the Bonos [26]. *N. latifolia* is a shrub with green leaves and multiple stems that is found in tropical Africa and Asia [27]. *N. latifolia* is distributed in the Savannah woodlands and the tropical rainforest of the Western and Central parts of Africa [8]. In Ghana, it is widely distributed in the Togo Plateau Forest Reserve in the Volta Region [28]. The plant measures about 20 ft tall in the Savanna woodland and about 100 ft tall in the forest zone. It has dark upper surface leaves which are acuminate, short, glabrous, opposite, and glossy green. The plant bears white, sweet-scented flowers and has a dark grey to brown cracked stem with a fibrous reddish slash [8,29]. Figure 1 shows images of various parts of *N. latifolia*.

N. latifolia is used for a wide range of therapeutic purposes among the indigenes of West Africa. The plant is used for treating infectious ailments, including yellow fever, gonorrhoea, diarrhoea, measles, HIV/AIDS, typhoid fever, helminthiasis, and malaria. Of the many NTDs, *N. latifolia* is reported to be used in the treatment of leprosy and filariasis (helminthiasis) [5,15,30,31]. The plant is also used

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Table 5. Pharmacological Activities of Bioactive Compounds in N. latefolia

Pharmacological Activity	Compound(s) responsible	Plant Part/ Extract	Reference
Antiplasmodial Activity	Strictosamide	Leaves/ Aqueous	[111]
Anti- inflammatory Activity	Quercetin	Leaves/ Methanol	[97]
	Gamma-sitosterol; 2- Methoxy-4 –vinylphenol; Phytol (3,7,11,15-tetramethyl-2-hexadecen-1-ol); Palmitic Acid (Hexadecanoic acid); α-linolenic acid (9,12,15-octadecatrienoic acid); Hexadecanoic acid, 2-hydroxy-1-(hydroxymethyl) ethyl ester	Leaves/ Ethanol	[131]
Anticancer Activity	Quercetin	Leaves/ Methanol	[97]
	Stigmasterol	Leaves/ Ethanol	[131]
	β-carotene; Lycopene	Leaves/ Ethanol	[105]
Antibacterial Activity	Isoquercitrin (quercetin-3-O-β-glucopyranoside); 3,5-O-dicaffeoylquinic acid	Leaves/ Methanol	[97]
	2,4-Dihydroxybenzoic acid; Farnesol acetate Cis-2-decenoic acid; Phytol (3,7,11,15-tetramethyl-2-hexadecen-1-ol)	(Leaf, stem bark)/ methanol	[100]
	Quinovic acid; Strictosamide.	Roots/ Ethyl acetate	[103]
	3,4-dihydroxybenzoic acid	Roots/ Methanol	
Antioxidant Activity	Isoquercitrin (quercetin-3-O-β-glucopyranoside); 3,5-O-dicaffeoylquinic acid; Quercetin; Chlorogenic acid (3-caffeoylquinic acid); Caffeic acid (trans-3,4-dihydroxycinnamic acid)	Leaves/ Methanol	[97]
	Palmitic Acid (Hexadecanoic acid), 2-hydroxy-1-(hydroxymethyl) ethyl ester; linoleic acid (9,12-octadecadienoic acid); Campesterol; 2- Methoxy-4–vinylphenol; Stigmasterol; Triethyl citrate	Leaves/ Ethanol	[131]
	Vitamin A; Vitamin C; Vitamin E	(Stem bark, Root bark)/ Ethanol	[139]
Antifungal Activity	Strictosamide; Quinovic acid	Roots/ Ethyl acetate	[103]
	3,4-dihydroxybenzoic acid	Roots/ Methanol	
	Strictosamide; Naucleamide A; Naucleamide F; Quinovic acid-3-*O*-β-rhamnosylpyranoside; Quinovic acid 3-*O*-β-fucosylpyranoside	Roots/ Ethanol	[140]
Hepatoprotective Activity	Pentanoic acid, 4-oxo-, ethyl ester; Stigmasterol; α-linolenic acid (9,12,15-octadecatrienoic acid); linoleic acid (9,12-octadecadienoic acid)	Leaves/ Ethanol	[131]
Antidiabetic Activity	Quinic acid; Phytol; Stigmasterol; Gamma-sitosterol; Phytol (3,7,11,15-tetramethyl-2-hexadecen-1-ol); Stearic acid (Octadecanoic acid);	Leaves/ Ethanol	[131]
Antiarthritic Activity	Phytol (3,7,11,15-tetramethyl-2-hexadecen-1-ol); α- linolenic acid (9,12,15-octadecatrienoic acid)	Leaves/ Ethanol	[131]
Hypocholesterolemic Activity	Palmitic acid (Hexadecanoic acid); Campesterol; Stigmasterol; Linoleic acid (9,12-octadecadienoic acid); α-linolenic acid (9,12,15-octadecatrienoic acid);	Leaves/ Ethanol	[131]
Antiandrogenic Activity	Palmitic Acid (Hexadecanoic acid); linoleic acid (9,12-octadecadienoic acid)	Leaves/ Ethanol	[131]
Anti- Glutathione S-transferase Activity	Strictosamide; Naucleamide F	Roots/ Ethanol	[140]
Analgesic Activity	Tramadol	Roots/ Methanol	[132]

in the treatment of non-infectious ailments, digestive disorders, disorders of cardiovascular and metabolic functioning, reproductive disorders, skin disorders, pain, respiratory disorders, and eye conditions [30,32-40]. Tables 1-3 provide detailed uses of *N. latifolia* in the treatment of various diseases. *N. latifolia* is indicated for the treatment of malaria among the indigenes of Ghana [9,10,41,42], Nigeria [43-49], Togo [50-52], Mali [14,17,53], Guinea [54,55], Sierra Leone [56,57], Benin [34], Burkina Faso [31], Cameroon [58] and Cote d'Ivoire [17]. The stem, leaves, roots, stem bark, and root bark are commonly used. These parts are used either alone or in combination with other plants in the preparation of decoctions, macerations, infusions, or tinctures [48]. The preparation is administered orally throughout all these countries. Details of the use of *N. latifolia* in the treatment of malaria are provided in Table 1. The plant is used as a remedy for dermatological disorders [59,60], itching [30,61], wounds [62], infantile dermatosis

[63], scalp infection [64] and burns [65]. Detailed uses of *N. latifolia* in the treatment of these skin conditions are provided in Table 2. Different parts of *N. latifolia* are used for the treatment of abdominal pains [14,31,35,65], headache [14] and backache [66]. Detailed uses of the plant in the treatment of these conditions are provided in Table 3. Preparations made from the roots, stem, leaves, and bark are used for treating helminthiasis in Nigeria [21,32,67], Ghana [15], Togo [68] and Sierra Leone [56], and specifically for treating filariasis in Nigeria [30]. In Ogbomoso and Edo states of Nigeria, preparations from the roots, leaves, stem, and bark of the plant are used to treat high blood pressure [43,46,69]. In the Ouémé region of Benin, root decoction is also administered orally to treat hypertension [70]. Also, *N. latifolia* is known as a remedy for hypertension in Accra, Ghana [71]. Decoction prepared from the stem bark of *N. latifolia* is administered as a cure for diabetes in Cote d'Ivoire [72] and Guinea [37]. The roots are reportedly used for the treatment of diabetes in Nigeria [43] and Benin [73].

Different parts of the plant are used as a remedy for fever in Ghana [9] and in various states of Nigeria [43,62,74], in particular the people of Tivland who rank it as the first choice of remedy for fever management [40]. The stem, bark, root, and fruit are used to treat stomach ailments in Cameroon [75], Nigeria [62,74] and Togo [52]. Infusion and decoction of the roots of *N. latifolia* are used to treat female infertility in Togo [52], Nigeria [76] and Burkina Faso [31]. The root, bark, and stem of *N. latifolia* are used to cure gastric ulcers in Nigeria [77-79]. The preparations from the stem and bark are used in the treatment of jaundice among the indigenes of the Accra metropolis, Ghana [9] and in parts of Nigeria [62,80,81]. Maceration of the roots of the plant is administered orally as a remedy for asthma [82]. Decoctions of the inner bark, stem, leaves, sap, fruit, root, and root bark are administered orally for the treatment of cough in Nigeria [36,62,83]. Sap from the stem and leaves of *N. latifolia* are reported to be used in Sierra Leone [56] and Cote d'Ivoire [39] for the treatment of eye conditions such as conjunctivitis, respectively. The root and bark of *N. latifolia* are used to remediate menstrual disorders in Nigeria [62,84] and Benin [85]. In Nigeria, decoctions and macerations of parts of *N. latifolia* are taken to treat yellow fever [30,49]. Decoction of the roots of *N. latifolia* is used as a cure for gonorrhoea in Nigeria [47,86]. Preparations of the roots, leaves, stem, and bark are either taken orally or used as enemas for the treatment of haemorrhoids by indigenes of the Tem tribe in Togo [52] and in parts of Nigeria [62]. The roots, leaves, and bark of *N. latifolia* are used as a remedy against urine retention in Burkina Faso [31] and Nigeria [32]. Male sexual dysfunction is treated in Nigeria using an alcohol infusion of the root bark [38] and in Mali using the root decoction [14].

The leaves of *N. latifolia* are known for the treatment of dysentery in Sierra Leone [56] and diarrhoea among the indigenes of Abidjan in Cote d'Ivoire [33]. The leaves of *N. latifolia* are claimed to be used for the treatment of HIV/AIDS in Nigeria [87]. The inner bark, stem, sap, roots, root bark and fruit of *N. latifolia* are reported among the inhabitants of Lagos in Nigeria for the treatment of measles [62]. The bark and roots of *N. latifolia* are prepared into decoctions and used for the treatment of typhoid fever in Nigeria [49] and in the Accra metropolis of Ghana [9]. The roots and leaves are reportedly used for the treatment of leprosy among the indigenes of the Baskoure, Kourittenga Province of Burkina Faso [31]. The stem, fruits and bark are used for the treatment of oral thrush [62]. In Nigeria, the stem of *N. latifolia* is chewed as a remedy for oral disorders [88]. The leaves and roots have been reported for use in the treatment of hernia in Burkina Faso [31]. A decoction prepared from the leaves is administered orally to cure cancer in Nigeria [89]. Indigenes of Togo administer root decoctions orally to treat Alzheimer's disease and Parkinson's disease [90].

In-vivo and in-vitro studies have been performed using extracts from parts of *N. latifolia* to investigate its pharmacological potential. The extracts of the various parts of the plant have been shown to exert anticonvulsant [91], antidepressant [92], antidiarrhoeal [93], antihypertensive [94], anti-inflammatory [95], antimicrobial [29,74, 96-104], antioxidant [97,105-107], antiplasmodial [108-114], antipyretic and antinociceptic [115,116], anti-ulcer [77,78,117,118], anxiolytic [91,92], hepatoprotective [119, 120], larvicidal and ovicidal [32,121,122], hypercholesterolaemic [123-125], hypoglycaemic [27,126-129], myorelaxant [92] and sedative [91] activities. Many of these pharmacological studies have been performed to scientifically prove the efficacy in ethnomedicinal uses of the various parts of the plant. Bioactive compounds are the specific compounds present in parts of plants that are responsible for particular biological or pharmacological activities. Table 5 indicates the active compounds present in specific parts of *N. latifolia*, the pharmacological activities they account for, and the extraction media used.

DISCUSSION

N. latifolia Smith has numerous ethnomedicinal uses in many West African countries, including Ghana, Togo, Mali, Sierra Leone, Burkina Faso, Cote d' Ivoire, Benin, Cameroon, Guinea, Cote d'Ivoire, and Nigeria [8-10,14,17,31,34,41-58,130]. Extracts of the roots, stem, bark, and leaves have demonstrated pharmacological activities that confirm some of the ethnomedicinal uses. Additionally, bioactive compounds, which account for a number of proven activities, have been isolated and characterized. The use of this plant as an antimalarial [31,53] is justified by tests performed by Anowi FC, Chibueze I [113] and Udobre AS, Udobang JA [110] using aqueous and methanolic leaf extracts, respectively. The extracts demonstrated a significant reduction in parasitaemia in laboratory mice. Strictosamide, a bioactive compound isolated from aqueous leaf extract, accounts for the anti-plasmodial activity [111]. Also, decoctions prepared from the leaves are administered as a cure for diabetes in Cote d'Ivoire [72] and Guinea [37]. This is justified by tests performed by Ezekwesili and

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Ogbunugafor [127] and Gidado and Danladi [126] using aqueous and ethanolic leaf extracts, respectively. The extracts caused a significant reduction in blood glucose levels in diabetic rats. Quinic acid, phytol, and stigmasterol are bioactive compounds isolated from ethanolic leaf extract that have been proven to be responsible for hypoglycemic activity [131]. Oral thrush is a fungal disease remediated in Nigeria using stem, root, and bark preparations of *N. latifolia* [62]. The antifungal activity of the plant is proven by tests performed by Ezem and Akpuaka [103] using ethyl acetate and methanolic extracts of the roots. Quinovic acid, Naucleamide A and Naucleamide F are components isolated from ethanolic and ethyl acetate root extracts and are responsible for the antifungal activity [103]. Tramadol, a widely known synthetic analgesic, was recently isolated from the methanolic root extract of the plant [132] and may possibly account for the ethnomedicinal use of the plant for the treatment of headaches in Mali [14] and backache in Nigeria [66]. Bacterial infections such as gonorrhoea and typhoid fever are treated in Nigeria using root and leaf decoctions [47,49]. Methanolic and ethanolic extracts of the leaves have demonstrated potent antibacterial activity using the agar-well-diffusion method [97,99]. Bioactive compounds responsible for the antibacterial activity include isoquercitrin, farnesol acetate, and cis-2- decanoic acid [97,100]. Quercitin, gamma-sitosterol, palmitic acid, and alpha-linolenic acid are anti-inflammatory compounds isolated from ethanolic and methanolic leaf extracts [97, 131] and whose potency has been proven using the egg-albumin-induced inflammation model in rats [95]. These tests justify the ethnomedicinal use of the plant in treating conjunctivitis [39].

Although pharmacological test models have been developed to demonstrate the antidepressant, anxiolytic, anticonvulsant, antihypertensive, anti-ulcer, antipyretic, and myorelaxant activities of the plant, specific bioactive compounds that account for these activities have not been identified and isolated. Furthermore, ethnomedicinal uses of the plant as a treatment for female infertility, male sexual dysfunction, urine retention, HIV/AIDS, hernia, Parkinson's, and Alzheimer's disease await scientific validation and, therefore, remain anecdotal. Of the many NTDs, *N. latifolia* is reported to be used in the treatment of leprosy and filariasis (helminthiasis) [5,15,30,31]. In the ethnomedicinal uses of this plant in the treatment of leprosy [5,15,30,31] and helminthiasis across several West African countries [15,21,32,56,67,68], and its use in the treatment of filariasis, in particular in Nigeria [30], few studies exist on its efficacy. Further pharmacological studies must be performed to validate its ethnomedicinal use as a remedy for a number of ailments, including female infertility, male sexual dysfunction, urine retention, HIV/AIDS, hernia, Parkinson's, and Alzheimer's disease. Secondly, the specific bioactive compounds that account for the antidepressant, anxiolytic, anticonvulsant, anthelminthic, antihypertensive, anti-ulcer, antipyretic and myorelaxant activities of the plant remain to be isolated. Finally, there is a need for further clinical evaluation of the toxicity of parts of *N. latifolia* as a medicinal plant.

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Author contributions
Conceptualization was done by EOB and BA. BA EOB, ML and AG participated in the writing and editing of the manuscript. EOB, ML, AG, and BA reviewed the manuscript. All authors approved the manuscript.

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Data for this work is available upon reasonable request from the corresponding author.

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