Alstonia boonei De Wild (Apocynaceae) – A Review of Its Ethnomedicinal Uses, Phytochemistry and Pharmacological Activities

Nkeoma Nkasi Okoye[1#]; Joy Nwando Nwokoye[1] and Chukwuma O B Okoye[2]
[1] Department of Pure and Industrial Chemistry, Faculty of Physical Sciences, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria.
[2] Department of Pure and Industrial Chemistry, Faculty of Physical Sciences, University of Nigeria, Nsukka, Enugu State, Nigeria.
[#]Corresponding Author:
Dr. Mrs. Nkeoma Nkasi Okoye
Email: nkn.okoye@unizik.edu.ng
Phone Number: 08060182374

Abstract

Alstonia boonei De Wild belongs to the family Apocynaceae. Its leaves, stem bark, root bark and sometimes, the stem latex have been traditionally used in parts of West Africa, for the management of various ailments ranging from malaria, hypertension to various forms of inflammation and cancer. It is also reputed for its use in the inducement of labour and in the management of post-partum haemorrhage. Its leaves, stem bark and root bark are rich in numerous secondary metabolites such as tannins, alkaloids, saponins, steroids, triterpenes, flavonoids, cardiac glycosides, cyanogenetic glycosides, carbohydrates and reducing sugars in various amounts. Calcium, phosphorous, iron, sodium, potassium and magnesium have also been found to be present in the plant parts. This review contains a fairly recent and distinct update on reports of the validated pharmacological activities as well as on the bioactive compounds already isolated and characterized from the leaves, stem bark ad root bark of *A. boonei* De Wild. It is expected that this review will provide a data base for reference and also stimulate a fresh interest in a coordinated pharmacological and phytochemical investigations into the reported folkloric uses of the various plant parts of *Alstonia boonei* De Wild.

Keywords: *Alstonia boonei* De Wild, Alstonia *spp*, Apocynacae, Egbu, Egbu-ora, Ahun, secondary metabolites, pharmacological activities.

INTRODUCTION

The 21st century has witnessed a high rate of technological advances in science and technology and drug discovery is not left behind. This is evidenced in the intensified on-going world-wide search for novel molecules of pharmacological importance from several biotopes. This ranges from search in the terrestrial and marine environment, to the harnessing of secondary metabolites of microbial origin including fungal endophytes. These have been supported with recent development in metabolomics and computer aided drug discovery, all with promising outcomes. Notwithstanding, in developing communities like in Africa and some parts of Asia, this coordinated search has not diminished the popularity of the traditional herbal medicine rather, it has remained a very popular source

of health-care for the common man. In Nigeria, for instance, just as in several other sub-Saharan African countries, there is a huge dependence on herbal remedies for the treatment of common ailments like malaria, typhoid fever, ulcers, diabetes etc. (Malan and Neuba, 2011) and in the maternal health care. This could be attributed to the inaccessibility of orthodox healthcare facilities by millions due to either their remoteness (Otu, 2018) or to the prevailing low socio-economic status of the end-users (James *et al;* 2018) or due to the fact that several herbal plants and mixtures are effective, affordable and easily available in the environment and even hawked on the streets. Massive and sometimes, unfortunately, misleading advertisements/ awareness campaigns by many herbal practitioners in countries like Nigeria have also become very common. This, too, may have largely contributed to this dependence.

Although there seems to be conflicting figures on the prevalent use of herbal medicines in Africa, its relatively high use has been reported (James *et al.;* 2018). In addition to this, the efficacy of herbal medicines when properly administered, must however not be underestimated. There is, therefore a need to harness the rich natural resources available in Africa which can contribute immensely in the fight against diseases particularly with the global concern of antimicrobial drug resistance (WHO, 2021). This will hopefully pave the way of incorporating herbal medicine into the global health care system.

Alstonia boonei is among the many plants reported to have remarkable pharmacological properties. *Alstonia boonei* De Wild (Apocynacae) is a common, large deciduous medicinal tree found in the lowlands and rain-forest areas of Nigeria as well as in various parts of Angola, Central African Republic, Ghana, Democratic Republic of Congo, Cote d'Ivoire (Adotey *et al*, 2012). It can grow as tall as 40 m, and can be branchless up to 27 m. Its cylindrical bole has high, narrow buttresses and can grow up to 100 cm in diameter (Burkil, 1985).

In Nigeria, *Alstonia boonei*, is known as Ahun in Yoruba, Egbu or Egbu-ora in Igbo, Ukhu in Edo and Ukpukunu in Urhobo, (Majekodunmia *et al*, 2008) while in Ghana, it is known as Onyame-dua in Ashanti and Emian in Cote d'Ivore (Malan and Neuba, 2011) and Ekouk in Fang (Obame-Engonga *et al,* 2019). In English, it is called cheese wood, pattern wood, or stool wood. Its trade name is Emien. The leaves, stem bark, root bark and sometimes, the stem latex of *A. boonei* are employed for the treatment of a variety of ailments in Africa. Its stem bark is popular in parts of West Africa as an anti-malarial remedy. In Ghana, it is grown because of its great ethnobotanical importance including its use as a spice crop (Opoku and Akoto, 2014)

In the recent past, quite a lot of reports have been presented on the ethnobotanical uses and preliminary phytochemistry and pharmacological properties. There were also reports on the isolation and detection of several bioactive compounds from the plant parts. This review report seeks to collate a fairly detailed update on the recent advances on the validation of the pharmacological and phytochemical properties of *Alstonia boonei*

De Wild (Apocynacae). Efforts have been made to clearly report both the ethnobotanical and pharmacological use of each reported fraction, distinguishing between the detected and isolated compounds while stating clearly whether such have been sourced from the leaves, stem bark and the root bark of *Alstonia boonei* De Wild (Apocynacae). This has been lacking in several earlier reports resulting in some sort of ambiguity in reports on the plant.

It is still worthy to note that in earlier reports originating from West Africa on *Alstonia boonei* De Wild, it has been referred to (in error) as *Alstonia congensis* (Adotey *et al*, 2012).

Ethnobotanical Uses of *Alstonia boonei* De Wild

The use of the various plant parts of a number of other plants with pharmacological importance in combination with *A. boonei* De Wild in the management of diverse ailments, has been established (Opoku and Akoto, 2014, Obame-Engonga *et al*, 2019). Traditionally, decoctions of either the leaves, stem bark, root bark and/or latex are taken alone or together with parts of other plants in herbal mixtures as a remedy for a diverse range of ailments in several parts of West Africa where it is found.

This prevalent and diverse folkloric use of *Alstonia boonei* De wild in various parts of Africa and Asia may have earned it the name Onyame Dua (God's tree) in certain parts of Ghana.

Although there are several reports of ethnobotanical uses as well as the pharmacological investigations carried out on *A. boonei*, it is unfortunate that numerous reports (especially, the earlier reports) did not clearly specify the plant part of *A. boonei* whose use was being reported. Some reports ambiguously, referred to the use of barks, making it difficult to note whether reference was being made to the stem bark or the root bark. Such reports, however, were excluded in this review.

The Leaves

In some parts of West and Central Africa a mash of the leaves *A. boonei* are applied topically to reduce swellings and for the treatment of sores, rheumatic pains, muscular pains and hypertension. A decoction of the leaves is also used in the treatment of resistant malaria (Omoya and Oyebola, 2019).

The Stem Bark

The stem bark *A boonei* is widely used in the management of dizziness, impotence, breast pain, rheumatic pain, tooth ache (Osadebe, 2003; Akinmoladun *et al*, 2007), malaria, as anti-venom against snake bites (Olanlokun and Olorunsogo, 2018, Osuntokun and Ajiga, 2020), and as arrow poison (Akinloye *et al*, 2013). Its use in the treatment of painful micturition and rheumatic conditions (Ojewole, 1984; Asuzu and Anaga, 1991), asthma (Akinmoladun, *et al*, 2007) have also been reported. The stem bark extracts of *A. boonei* is used to induce labour, remove retained placenta and also in the management post-partum haemorrhage (Uzor *et al*, 2017).

The Root Bark

The root bark of *Alstonia boonei* has been used, over the years, in the treatment of rheumatic and breast pain (Osadebe, 2003)

The Stem Latex

Its latex is usually boiled in water and drunk as remedy for fever in children, as a stimulant for lactation and also taken as a laxative (Adotey *et al*, 2012)

Combined Plant Parts

The leaves and latex of *A. boonei* De Wild are applied topically to reduce swellings as well as for the treatment of rheumatic pains. An infusion of the root and stem bark is taken as a remedy for asthma. A liquid made from the stem bark and leaves is drunk to treat impotence. In Cote d'Ivoire and Burkina Faso, it is applied topically to reduce oedema and to clear suppurate sores and exposed fractures.

A number of herbal mixtures containing either the plant parts of *A. boonei*, or in combination with parts of other plants has been used for the management of various ailments such as malaria and Typhoid fever (Etame *et al*, 2019), hypertension (Turkson *et al*, 2019) gastritis, pelvic and chest pains, skin infections, and cancers (Languon *et al*, 2018). However, it is impossible to trace the observed pharmacological activity of the mixture to either of the plant component by analyzing the mixture. Furthermore, some of the observed medicinal properties of the herbal mixtures could be as a result of synergy among various constituents and so cannot be directly traced to *A. boonei*.

Phytochemicals from *A. boonei* De Wild (Apocynacae).

The leaves, stem bark and root bark of *Alstonia boonei* De Wild are rich in tannins, alkaloids, saponins, steroids, triterpenes, cardiac glycosides, cyanogenetic glycosides, carbohydrates and reducing sugars in various amounts (Osadebe, 2003; Ojo *et al*, 2014; Opoku and Akoto, 2014; Akinnawo *et al*, 2017; Omoya and Oyebola, 2019; Ajose *et al*, 2019; Arogbodo, 2019). Significant amounts of calcium, phosphorous, iron, sodium, potassium and magnesium have also been reported to be present in some of the plant parts (Akinmoladun *et al*, 2007). The root bark has been shown to contain similar secondary metabolites to that reported for the stem bark (Opoku and Akoto, 2014; Klu *et al*, 2016; Omoya and Oyebola, 2019). Several bioactive secondary metabolites have been isolated and/or detected from different parts of the plant as shown in Table 1. The chemical structures of these compounds are also shown in Figure 1.

Table 1: Compounds isolated or detected from different parts of *A. boonei*

S/N	Part of Plant	Name of Compound	Class of Compound	Pharmacological Activity	References
1	Leaf	Quercetin-3-O-[α-L-rhamnopyranosyl(1→6)-β-D-glucopyranoside (**Rutin)**	Flavonoid	Antioxidant	Okoye and Okoye,

					2016 a (Isolated)
2	Leaf	Quercetin-3-O-[α-L-rhamnopyranosyl(1→6)-β-D-galactopyranoside]. **(Quercetin-3-O-robinobioside)**	Flavonoid	Antioxidant	Okoye and Okoye, 2016 a (Isolated)
3	Leaf	kaempferol-3-O-[α-Lrhamnopyranosyl(1→6)-β-D-glucopyranoside] (**Kaempferol-3-O-rutinoside)**	Flavonoid		Okoye and Okoye, 2016 a (Isolated)
4	Leaf	{Kaempferol-3-O-[α-Lrhamnopyranosyl(1→6)-β-D-galactopyranoside]}. **(Kaempferol-3-O-robinobioside)**	Flavonoid		Okoye and Okoye, 2016 a (Isolated)
5	Leaf	Quercetin-3-O-[α-L-rhamnopyranosyl(1→4)-β-D-glucopyranoside].	Flavonoid	Antioxidant	Okoye and Okoye, 2016 a (Isolated)
6	Leaf	Kaempferol-3-O-[α-L-rhamnopyranosyl(1→4)-β-D-glucopyranoside]	Flavonoid		Okoye and Okoye, 2016 a (Isolated)
7	Leaf	Quercetin-3-O-[α-L-rhamnopyranosyl (1→2) β-D-glucopyranoside]	Flavonoid	Antioxidant, Antimicrobial	Okoye and Okoye, 2016 a (Isolated)
8	Leaf	Quercetin-3-O-[α-L-rhamnopyranosyl(1→2)-β-D-galactopyranoside]	Flavonoid	Antioxidant, Antimicrobial	Okoye and Okoye, 2016 a (Isolated)
9	Leaf	5-caffeoylquinic acid **Chlorogenic acid**	Phenolic acid	Antioxidant	Okoye and Okoye, 2016 b (Isolated)
10	Leaf	4,5-dicaffeoylquinic acid	Phenolic acid	Antioxidant	Okoye and Okoye,

					2016 b (Isolated)
11	Stem bark	beta amyrin	Terpene	Anti-inflammatory	Okoye *et al*, 2014 (Isolated)
12	Stem bark	alpha amyrin acetate	Terpene	Anti-inflammatory	Okoye *et al*, 2014 (Isolated)
13	Stem bark	Alstiboonine	Indole alkaloid	Cytotoxicity	Balogun *et a*l, 2016 (Isolated)
14	Stem bark	N_{α}-formylechitamidine	Alkaloid		Oguakwa, 1984 (Isolated)
15	Stem bark	Echitamidine	Alkaloid	Antihypertensive	Oguakwa, 1984 (Isolated)
16	Stem bark	1, 4-Dioxacyclohexanedecane-5,16-dione	Fatty acid		Olanlokun *et al*, 2021 (Detected)
17	Stem bark	2-Oxodecanoic acid	Fatty acid		Olanlokun *et al*, 2021 (Detected)
18	Stem bark	Olivetol	Phenolic		Olanlokun *et al*, 2021 (Detected)
19	Stem bark	Xanthoxylin			Olanlokun *et al*, 2021 (Detected)
20	Stem bark	Nonanamide			Olanlokun *et al*, 2021 (Detected)
21	Stem bark	Funtumine	Steroid		Olanlokun *et al*, 2021 (Detected)
22	Stem bark	17-Hydroxylinoleic acid	Fatty acid		Olanlokun *et a*l, 2021 (Detected)

23	Stem bark	N-2-Hydroxypalmitoylsphingosine			Olanlokun *et al*, 2021 (Detected)
24	Stem bark	Stigmasterone	Steroid		Olanlokun *et al*, 2021 (Detected)
25	Stem bark	Oleanoic acid	Terpene		Olanlokun *et al*, 2021 (Detected)
26	Stem bark	Stigmasterol	Steroid		Kiganda, 2018 (Isolated) Olanlokun *et al*, 2021 (Detected)
27	Stem bark	Corosolic acid	Terpene		Olanlokun *et al*, 2021 (Detected)
28	Stem bark	Maslinic acid	Terpene		Olanlokun *et al*, 2021 (Detected)
29	Stem bark	B-D-Galactopyranoside, (3 B)-stigmast-5-en-3-yl,6-butanoate			Olanlokun *et al*, 2021 (Detected)
30	Stem bark	Lupeol Acetate	Terpene		Kiganda, 2018 (Isolated)
31	Stem bark	lichexanthone	Xanthone		Kiganda, 2018 (Isolated)
32	Stem bark	Cycleucalenol	Terpene		Kiganda, 2018 (Isolated)
33	Stem bark	Phenanthridine-6(5H)-one	Alkaloid		Kiganda, 2018 (Isolated)
34	Stem bark	Ursolic acid	Terpene		AlQathama *et al*, 2020 (Detected)

35	Stem bark	Quercertin	Flavonoid		AlQathama *et al*, 2020 (Detected)
36	Root/stem bark	Lupeol	Terpene		Kiganda, 2018, (Isolated) AlQathama *et al*, 2020 (Detected)
37	Root bark	B-sitosterol	Steroid		Kiganda, 2018 (Isolated)
38	Root/stem bark	Echitamine	Alkaloid	Antihypertensive	Ojewole, 1984; Kiganda, 2018 (Isolated)
39	Stem bark	Tetrahydro-4-((E)-7-hydroxy-10-methoxy-6,14-dimethyl-15-m-tolylpentadec-13-enyl)pyran-2-one		Antimalarial	Olanlokun *et al*, 2019 (Isolated)
40	Stem bark	tetrahydro-4-(7-hydroxy-10-methoxy-6, 14-dimethyl-15-m-tolylpentadec-13-enyl) pyran-2-one isobutyryl acetate			Olanlokun *et al*, 2020

Pharmacological activities of *A. boonei*

Several attempts have been made to validate the claimed ethnomedicinal uses of *A. boonei.* These have led to many reports on pharmacological activities of the different plant parts of the plant as discussed in the subsequent subsections.

Anti-cancer activity

Methanol extract of *A. boonei* stem bark has been found to be cytotoxic (Ohiagu *et al*, 2020) against the human colon carcinoma. Several reports have attributed the observed cytotoxic effects to the presence of Lupeol (Kiganda, 2018), Ursolic acid and Quecertin (AlQathama *et al*, 2020), echitamine (Kiganda, 2018) and Alstiboonine (Balogun *et al*, 2016) in stem bark, eugenol in leaf as well as 1, 2-benzenedicarboxylic acid present in the root bark extracts (Ohiagu *et al*, 2020). In another report, CH_2Cl_2/MeOH extracts of the stem and root barks of *A.boonei* was shown to have remarkable cytotoxic

tendencies towards some of the tested human cancer cell lines. The extract, however, was not selective as it was also found to be toxic to the normal human cells (Kiganda, 2018). *A. boonei* is present in a Ghanaian herbal product Kantinka Herbaltics popularly used for management of cancer although the plant part used was not indicated. This herbal product, when investigated, was found to be cytotoxic against some human cancer cell lines (Languon *et al*, 2018).

Anti-inflammatory activity

Independent analyses of the anti-inflammatory activity of the methanol extract, (Iniaghe *et al*, 2012) as well as the aqueous and ethyl acetate (Akinnawo *et al;* 2017) fractions of its leaves yielded profound dose dependent activity using Wister albino rats induced with rat paw oedema.

Similar observations were made from its methanol stem bark extracts (Olajide *et al*, 2000). Additionally, the solvent fractions such as the n-hexane fraction (Olanlokun *et al*, 2021) and compounds (Okoye *et al*; 2014) display remarkable anti-inflammatory activity. This activity was also reported of the root bark (Osadebe, 2002), from its methanol extract. These independent reports could lend credence to the folkloric use of *A. boonei* De Wild in the treatment of tooth ache, breast, rheumatic and muscular pains. In other studies, the analysis of the methanol leaf (Iniaghe *et al*, 2012) and stem bark (Olajide *et al*, 2000) and ethanol root bark (Osadebe, 2003) extracts of *A. boonei* showed a significant and dose-dependent analgesic activity, hence further justifying its traditional use as a pain reliever.

Anti-malarial activity

The results of a number of investigations on the antimalarial activity of aqueous and methanol extract *A. boonei* leaves revealed a dose dependent chemo-suppression and cure of parasitaemia of *P. beghei* infected rodents (Dibua *et al*, 2013a; Omoya and Oyebola, 2019) which were comparable to the antiplasmodial effect of Chloroquine (Imam *et al*, 2017). This activity was also confirmed using other models (Dibua *et al*, 2013b). It was however noted that synergy could be a key player in the observed anti-plasmodial activity. Similar results were obtained with ethanol (Iyiola *et al*, 2011, Otuu *et al*, 2020) methanol; (Omoya and Oyebola, 2019) and aqueous (Ebiloma *et al*, 2012, Omoya and Oyebola, 2019) stem bark extracts. These reports could be taken as the justification for the folkloric use of the plant parts of in the treatment of malaria.

Anti-helminthic activity

The Anti-helminthic activity of the roots and stem bark of *A. boonei* was investigated using a surrogate model, a closely related adult Indian earthworm (*Pheretima posthuma*) as well as on the human intestinal roundworms (Klu *et al*, 2016). The results showed that the extracts exhibited a dose dependent activity against the tested worms, with the stem bark extract possessing higher activity. The report also suggested that the observed activity could be as a result of the presence of alkaloids.

An earlier trial on the common earth worm (*Lumbricus terretris)* reported that the aqueous and ethanol extracts possess anti-helminthic activity and suggested its

investigation with human intestinal worms (Danqua *et al,* 2012). Aqueous extracts of *A. boonei* stem bark when tested on *Trichostrongylus* infective larvae, also gave positive anti-helminthic results (Asuzu and Njoku, 1996).

Anti-microbial activity

Both methanol (Irulandi *et al*., (2017) and ethanol extracts (Arogbodo, 2019) of *A. boonei* leaves and stem bark (Ajose *et al,* 2019; Obame-Engonga *et al,* 2019) are generally reported to show a mild to moderate antimicrobial activity. In a Similar study, an ethanol fraction of a benzene extract of the leaves of *A. boonei* gave MIC values of 12.5 mg/mL against common strains such as *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Proteus mirabilis* (Okwu and Ighodaro, 2010).

However, reports on the optimization of the antimicrobial solvent fractions of *A. boonei* stem bark extracts revealed that the ethanol fractions exhibited the lowest MIC values compared to the chloroform fractions (Amole and Ilori, 2010; Ogueke *et al* , 2014).

The reports on the antimicrobial activity of the aqueous and ethanol root extracts of *A. boonei* showed significant inhibition of common strains of bacteria and fungi viz *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* as well as *Candida albicans*. Ethanol extract, however, was reported to show less MIC values than the aqueous root extracts. (Opoku and Akoto, 2014). The reported antimicrobial activity may, thus, serve as a pharmacological basis for the use of *A.boonei* in the treatment of Typhoid fevers, sores, tooth ache and diarrhea (Melogmo *et al,* 2020).

Antioxidant activity

The leaf extracts and fractions of *A. boonei* have been reported to show a dose dependent antioxidant activity using various models (Omoregie *et al;* 2014). In some studies using the DPPH free radical scavenging model, the antioxidant potentials of the leave were further traced to the presence of two caffeic acid derivatives, 5- caffeoylquinic acid (Chlorogenic acid) and 4,5-dicaffeoylquinic acid and several flavonoid glycosides, all isolated from the leaves (Okoye and Okoye, 2016a, 2016b)**.**

Similarly, the stem bark extracts of *A. boonei* was investigated using the DPPH radical scavenging activity model but found to possess a low antioxidant activity (Akinmoladun *et al,* 2007), an indication of the possibility, that the numerous pharmacological activities observed in *A. boonei* stem bark could be attributed to synergy and to the presence of other phytoconstituents including minerals which are also present. This report, however, contradicts the conclusion by Nkono *et al* (2014) that the stem bark extract shows antioxidant activity.

The root bark extract of *A. boonei* and some isolated compounds also displayed good antioxidant activity in DPPH free radical scavenging model (Obiagwu *et al,* 2014). This consistent antioxidant activity of extracts of different plant parts of *A. boonei* has, therefore been suggested (Obiagwu *et al*, 2014) to be responsible for the diverse useful medicinal properties of *A. boonei*, justifying

its common usage for the management of a wide range of ailments.

Anti-diabetic activity

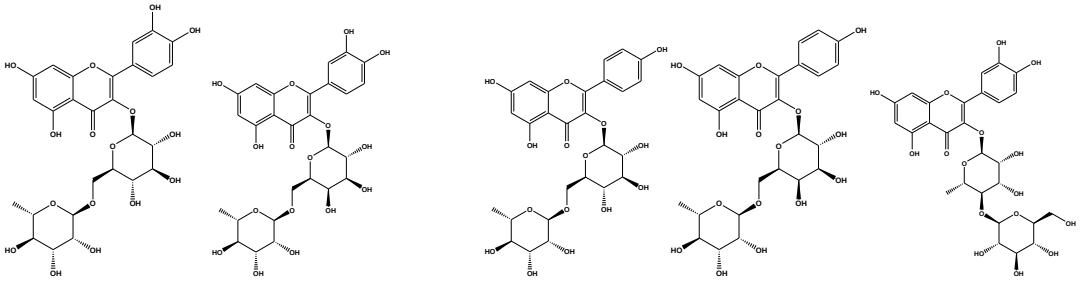
Reports on the antidiabetic studies showed that the extracts of the leaves, stem bark (Akinloye *et al*, 2013); Nkono *et al*; 2014) and the roots of *A. boonei* display good hypoglycemic effect on rat models, with the stem bark extract showing the greatest activity (Osadolor *et al* 2015; Owolabi *et al*, 2014)

Anti-ulcer activity

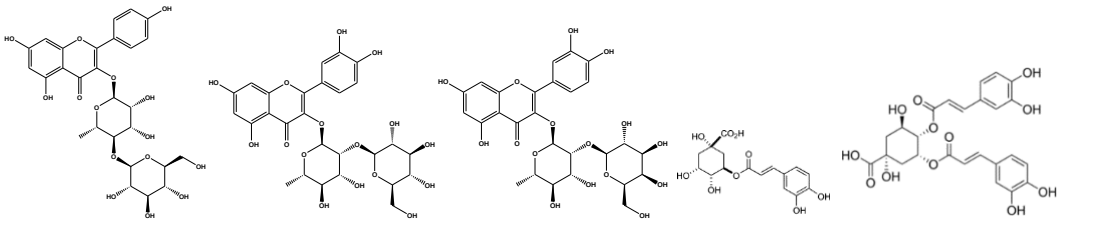
Studies on the antiulcer activity of the aqueous (Christophe *et al*, 2016) and methanol (Adjouzem *et al*, 2020) stem bark extracts of *A. boonei* showed that the extracts have significant inhibition and healing effects on test rats.

Central nervous system depressant effect

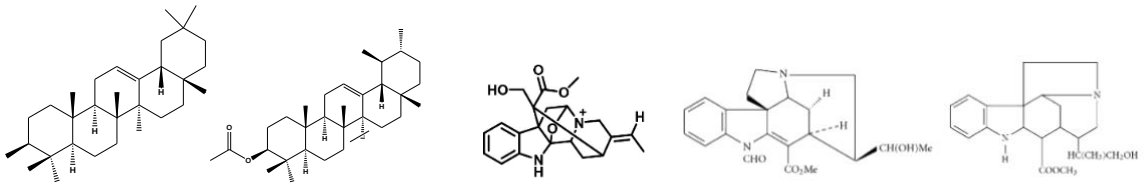
In several other studies, both aqueous and methanol extract of *A. boonei* leaves and stem bark resulted in drowsiness among the test mice (Omoya and Oyebola, 2019, Dibua *et al*, 2013a, Idowu *et al*., 2010). This could be linked to a central depressant effect and may explain the traditional use of *A. boonei* stem bark in the management of mental health conditions.



1 2 3 4 5



6 7 8 9 10



11 12 13 14 15

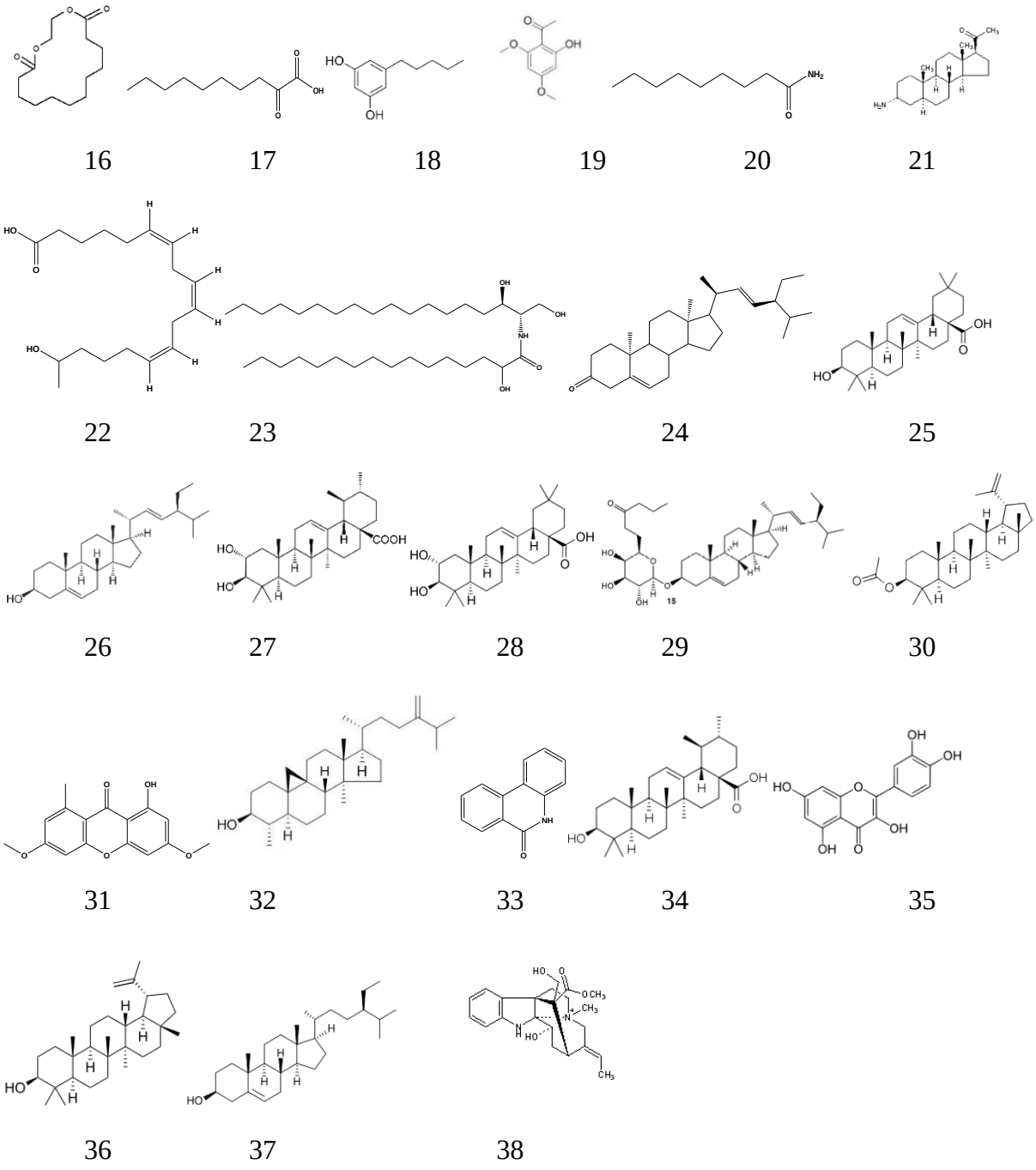


Figure 1: **The chemical structures of the compounds isolated or detected from different parts of *A. boonei***

Cholesterol lowering effect

The cholesterol lowering effect of *A. boonei* stem bark extract has also been established (Kehinde *et al*, 2016) and this was supported by the findings of another independent research (Gabriel *et al*, 2007). *A. boonei* has also been mentioned as a constituent of a very

effective antihypertensive herbal mixture although the activity could not be directly linked to either *A. boonei* or the co-ingredient.

Insecticidal activity

Aqueous extract of the leaves and stem bark of *A. boonei* were found to be significantly toxic to the larvae of the pink stalk borer, *Sesamia calamistis* Hampson (Oigiangbe *et al,* 2007). In another report, the alkaloid-rich leaf extract was shown to exhibit good larvicidal effect against the legume pod borer, *Maruca vitrata* Fabricius (Oigiangbe *et al,* 2013). Ethanol extract of the leaves of *A. boonei* has also been reported to display larvicidal activity against *Anopheles arabiensis* mosquito (Omoya *et al.;* 2012). Other studies have shown that the acetone fractions of the leaves, stem bark and root bark, alstodine and alstonine (compounds previously isolated from the *A. boonei* stem bark) exhibited various degrees larvicidal and pupacidal activities as well as fumigant and insect repellant activities against *Anopheles gambiae* (Ileke and Ogungbite, 2015; Bassey and Izah, 2017).

Oxytocic effect

The oxytocic activity of various fractions of *A. boonei* stem bark has been validated thereby justifying its folkloric use in the inducement of labour and as an afterbirth for the removal of placenta (Uzor *et al;* 2017). The observed oxytocic effect, however, implies that administration of herbal remedies containing *A. boonei* leaf, stem bark and the root bark extracts should be discouraged during pregnancy as this may result in termination of the pregnancy.

Studies on Toxicity of *A. boonei*

According to Dibua *et al,* (2013a), doses of *A. boonei* ethanol leaf extracts as much as 5,000 mg/kg produced a reduced activity in experimental rats accompanied with a mild drowsiness and weakness but no fatality was recorded during a 4-day observation period. However much higher doses and even prolonged use of much lower doses of the aqueous leaf extract resulted in hepatotoxicity (Oshomoh and Imoyera, 2020).

Aqueous extracts of the stem bark of *A. boonei* showed LD_{50} values of greater than 5000 mg/Kg in Wister rats (Iyiola *et al,* 2011, Nkono *et al,* 2015). In other studies, the extracts were also found to be both nephrotoxic and hepatotoxic even at moderate doses (Ileke *et al,* 2014, Oze *et al,* 2017, Olalokun and Olorunsogo, 2018, Osuntokun and Ajiga, 2020) with toxicity occurring over prolonged usage of lower doses (Oze *et al,* 2007). Both leaf and stem bark (and most likely root bark) extracts of *A. boonei* De Wild should, therefore, be used with caution even at lower concentrations but for longer periods (Oshomoh and Imoyera, 2020). These results on hepatotoxicity, however, sharply contrasted the report of the hepatoprotective effect of the ethanol fraction of *A. boonei* (Ojo *et al*, 2014).

Further Advances in *A. boonei* Research

Endophytic Fungi studies

Endophytic fungi cultured from different plant parts of *A. boonei* can hitherto best be described as largely unexplored. However, a few investigations show anti-microbial endophytic metabolites both from stem bark

(Tolulope *et al,* 2015) and the leaf extract (Demeni *et al,* 2021) of *A. boonei*. Fortunately, endophytic fungi have been reported to produce new secondary metabolites (Liu and Liu, 2018) promising to yield a unique set of new molecules from *A. boonei* with an entirely different set of pharmacological activities.

Formulation studies

Not so many studied have been reported on the formulation of extracts of *A. boonei* into different dosage forms. There is, however, a report on the formulation of tablets for easy administration from the ethanol extract of the stem bark (Majekodunmi *et al,* 2008, Chime *et al,* 2013). In Ghana, a herbal formulation (Kantinka Herbaltics (K-HER)) containing a mixture of *Spathodea campanulata*, *Mangifera indica*, and *Alstonia boonei* is marketed for the management of gastritis, pelvic and chest pains, skin infections, and cancers (Languon *et al,* 2018)

Conclusion

The leaves, stem bark and root bark of *Alstonia boonei* De Wild Apocynaecae are well known in several parts of West Africa and some parts of Asia for their ethnobotanical use in the treatment of various ailments and as an ingredient of several herbal remedies. Results of the investigation of the crude aqueous and or methanol/ethanol extracts have been presented in this review. This review also features a few reported pharmacological activities which have been traced down to isolated compounds or groups of compounds. It is also worthy to note that isolation of component compounds, in an attempt to trace reported activities, have, on a number of occasions resulted in a loss (or reduction) of pharmacological activity (Rasoaaivo *et al,* 2011) thus, authenticating the use of formulations of solvent extracts or fractions as remedies, rather than formulations of pure drugs. This could be attributed to loss of synergistic effects of the constituents upon isolation and purification. Extracts of *A. boonei* leaves, stem and root barks, should be used with caution as toxicity has been observed at very high doses as well as prolonged use in low doses. The oxytocic effect should also be put into consideration during administration.

Alstonia boonei De Wild has been shown to possess great prospects for further *in silico*, *in vitro*, *in vivo* and clinical studies. These are already in progress (Olanlokun *et al,* 2020).

Conflict of Interest

The authors declare no conflicts of interest.

References

Adjouzem, C. F.; Gilbert, A.; Mbiantcha, M. Nana, W. Y. Mba, V. M. M.; Nguemnang, S. F. D.; Tsafack, E. G. and Atsamo, D (2020) Effects of Aqueous and methanolic extract of stem bark of *Alstonia boonei* De Wild. (Apocynaceae) on Dextran Sodium Sulfate-induced Ulcerative Colitis in Wister Rats. *Evidence-based Compl and Alt Med*. 2020(12):1-15.

Adotey, J. P. K.; Adukpo, G.; Boahen, Y. O. and Armah, F. A. (2012). A Review of the ethnobotany and pharmacological importance of *Alstonia boonei* De Wild

(Apocynaceae). *Int Scholar Res Not* 1:1–9.

Ajose, D. J.; Onifade, O. F. and Wemambu I. I (2019) phytochemical analysis and in vitro antibacterial evaluation of leaf and bark extracts of *Alstonia boonei. Afr. J. of Pharm and Pharmacol.* 13(17):287-291

Akinloye, O. A.; Oshilaja, R. T.; Okelanfa, O. A.; Akinloye, D. I. and Idowu, O. M. O. (2013) Hypoglycemic activity of *Alstonia boonei* stem bark extract in mice. *Agric and Biol J of N Amer* 4(1): 1-5.

Akinmoladun, A. C.; Ibukun, E. O.; Afor, E.; Akinrinlola, B. L.; Onibon, T. R.; Akinboboye, A. O.; Obuotor, E. M. and Farombi, E. O. (2007) Chemical constituents and antioxidant activity of *Alstonia boonei. Afr Jl of Biotech* 6(10):1197-1201.

Akinnawo, O. O.; Anyasor, G. N.; Osilesi, O. (2017) Aqueous fraction of *Alstonia boonei* de Wild leaves suppressed inflammatory responses in carrageenan and formaldehyde induced arthritic rats. *Biomed & Pharmacother* 86:95-101.

AlQathama, A.; Ezuruike, U. F.; Mazzari, A. L. D. A.; Yonbawi, A.; Chieli, E. and Prieto, J. M. (2020) Effects of Selected Nigerian Medicinal Plants on the Viability, Mobility, and Multidrug-Resistant Mechanisms in Liver, Colon, and Skin Cancer Cell Lines. *Front in Pharmacol* 11:546439

Amole, O.O. and Ilori, O.O. (2010) Antimicrobial activity of the aqueous and ethanolic extracts of the stem bark of *Alstonia boonei. Int J of Phytopharmacol* 1(2):119-123.

Arogbodo, J. O. (2019) Phytochemical Screening and Antimicrobial Effect of Ethanolic Leaf Extract of *Alstonia boonei* De Wild (Apocynaceae) on some Selected Pathogenic Micro-organisms. *Int J of Curr Microbiol and Appl Sci* 8(7):1373-1379

Asuzu, I. U. and Anaga, A. 0. (1991) Pharmacological screening of the aqueous extract of *Alstonia boonei. Fitoterapia*. 62:411-417.

Asuzu, I. U. and Njoku, C. J. (1996) The anthelmintic effect of *Alstonia boonei* bark and *Nauclea latifolia* leaf aqueous extracts on *Trichostrongylus* infective larvae. *Fitoterapia* 67(3):220-222

Awodele, O.; Osunkalu, V. O.; Akinde, O. R.; Teixeira da Silva, J. A.; Okunowo, W. O.; Odogwu, E. C. and Akintonwa, A. (2010) Modulatory Roles of Antioxidants against the Aqueous Stem Bark Extract of *Alstonia boonei* (Apocynaceae)-induced Nephrotoxicity and Testicular Damage. *Int J of Biomed and Pharml Sci* 4:76-80

Balogun, O. S.; Ajayi, O. S. and Agberotimi, B. J. (2016) A cytotoxic indole alkaloid from *Alstonia boonei. J Biol Act Prod Fr Nat* 6(4):347-351.

Bassey, S. E. and Izah, S. C. (2017) Nigerian plants with insecticidal potentials against various stages of mosquito development. *ASIO J of Med & Health Sci Res (ASIO-JMHSR)*, 2(1):07-18

Burkill, H.M. (1985) The Useful Plants of West Tropical Africa. Royal Botanic Gardens, Kew, Richmond, Surrey, UK.

Chime, S. A.; Ugwuoke, E. C.; Onyishi, V. I.; Brown, S A and Onunkwo, G. C. (2013) Formulation and evaluation of *Alstonia boonei* stem bark powder tablets. *Indian J of Pharm Sci*. 75(2):226-230

Christophe, M.; Gaël, S.; Perfusion, A.; Olivier, E.; Lefils, B.; Nicaise, E.; François, E.; and Vernyuy, T. P. (2016). Anti-Ulcers properties and safety profile assessment of aqueous stem bark extract of *Alstonia boonei* De Wild (Apocynaceae) in rodents. *J of Intl Res in Med and Pharm Sci* 10(3):133-145.

Danquah, C. A.; Koffuor, G. A.; Annan, K. and Ketor, E. C. (2012). The anthelmintic activity of Vernonia amygdalina (Asteraceae) and *Alstonia boonei* De Wild (Apocynaceae). *J. Med. Biomed. Sci.* 1(1):21-27.

Demeni, P. C. E.; Betote, P. H. D.; Kom, C. W.; Tchamgoue, E. N.; Moni, E. D. F. N.; Maniepi, J. S. F. Agbor, G. A. and Nyegue, M. A. (2021) Endophytic Fungi from *Alstonia boonei* De Wild and *Greenwayodendron suaveolens* (Engl. and Diels) Verdc. subsp. *Suaveolens* Possess Inhibitory Activity against Pneumonia Causing Bacteria. *Evidence-Based Compl and Alt Med* 2021:1-10

Dibua, U. M.; Okeke, C. C.; Ugwu, C.; Kenechukwu, F. C. and Okorie, A. (2013a) *In vivo* antimalarial and cytotoxicity activity of ethanolic stem bark of *Petersianthus macrocarpus* and leaf of *Alstonia boonei* in experimental mice model *Int J Curr Microbiol App Sci* 2(12):354-368

Dibua, U. M.; Kalu, A.; Attamah, A. A.; Esimone, C. O. and Eyo, J. E. (2013b) In vivo and in vitro evaluation of the inhibitory effect of some medicinal plant extracts on haemozoin concentration. *Animal Res Int* 10(2):1699-1712

Ebiloma, G.; Amlabu, E.; Atanu, F. O.; Amlaby, W.; Aminu, R. (2012) Effects of the aqueous extracts of *Alstonia boonei* on the hematological profile of mice experimentally infected with chloroquine-sensitive strain of *Plasmodium berghei* NK-65 *Hematologia* 1(11)11-18

Etame, L. G.; Nda, M. J. P.; Okalla, E; Ndounda, H.; Sikadeu, S.; Tankeu, S. E.; Yinyang, J.; Ngene, J. P.; Ngoule, C. C.; Kidik, P. C. and Dibong, S. D. (2019) Evaluation of Bacterial Activity *in Vitro* on *Salmonella Enterica* of *Typhi* Stereotype of Drugs of Medicinal Plants, *Annickia*

Chlorantha (Oliv.) Setten & Maas, *Alstonia Boonei* De Wild and *Costus Afer* Ker Gawl Used In the Treatment of Typhoid Fever. *Saudi J of Biomed Res* 4(5):237-243

Gabriel, O.; Harrision, N.; Okey, O. and Ukoha, A. (2007) *Changes In Lipid And Haematological Profile Of Aqueous Ethanolic Extract Of Alstonia Boonei In Rats*. *The Internet J of Hematol*. 4(1)

Idowu, O. A.; Soniran, O. T.; Ajana, O. and Aworinde, D. O. (2010) Ethnobotanical survey of antimalarial plants used in Ogun State, Southwest Nigeria. *Afr. J. Phar. Pharmacol.* 4:55-60

Ileke D. K.; Odeyemi, O. O. and Ashamo, M. O. (2014) Toxicological and Histopathological Effects of Cheese Wood (*Alstonia boonei* De Wild) Stem Bark Powder used as Cowpea Protectant against Cowpea Bruchid, *Callosobruchus maculatus* (Fab.) [Coleoptera: Chrysomelidae] on Albino Rats. *Int J of Mol Med Sci*, 4(2)

Ileke, K. D. and Ogungbite, O. C. (2015) *Alstonia boonei* De Wild oil extract in the management of mosquito (*Anopheles gambiae*), a vector of malaria disease *J of Coastal Life Med*. 3(7): 557-563

Imam, A. A.; Atiku, M. K.; Muhammad, I. U.; Ezema, M. D.; Alhassan, A. J.; Idi, A.; Mohammed, A.; Abdullahi, H. and Alexander, I. (2017) In vitro Antimalarial Activity of Solvents Extracts of *Alstonia boonei* Stem Bark and Partial Characterization of Most Active Extract(s) *J of Pharm Res Int* 19(2):1-10,

Iniaghe, L. O.; Okpo, S. O.; Olung, J. E. and Eguae, A. A. (2012) Analgesic effect of methanol leaf extract of *Alstonia boonei* De Wild (Apocynaceae) *Trop J of Pharm Res* 11(5):793-798

Irulandi, K.; Geetha, S. and Mehalingam, P. (2017). Antimicrobial activity of selected Indian Folk medicinal plants: *Myristica fatua*, *Alstonia boonei*, *Helictress isora*, *Vitex altissima* and *Atalantia racemosa*. *Asian J of Pharml and Clin Res*. 10(2):277-280.

Iyiola, A. O; Tijani, A. Y. and Lateef, K. M. (2011) Antimalarial activity of the ethanolic stem bark extract of *Alstonia boonei* in mice *Asian J of Biol Sci* 4(3):235-243

James, P. B.; Wardle, J.; Steel, A. and Adams, J. (2018) Traditional, contemporary and alternative medicine use in Sub-Saharan Africa: A systematic review. *BMJ Global Health Journal* 3(5): **:**e000895.

Kehinde, A. J.; Adebayo, A. J.; Oluwadamilola, S. O and Arinola, A. A (2016) Stem Bark Extract from *Alstonia boonei* attenuates Cholesterol, Triglyceride and

Oxidative Damage via Low Immunohistochemical Expression in Small Intestinal Tract of Male Rats. *J Diabetes Metab*. 7:715. doi: 10.4172/2155-6156.1000715

Kiganda, E. (2018) Phytochemical Investigation of Alstonia boonei and Schizozygia coffaeoides for cytotoxic principles. (Unpublished Ph. D Thesis)

Klu, M. W.; Apenteng, J. A.; Mintah,D. N.; Addy, B. S.; Nyarko-Danquah, I. and Afriyie, S. B. (2016) In vitro anti-helminthic activity of the stem and root barks of *Alstonia boonei* De Wild. *J of Med Plants Res* 10(13):179-182

Languon, S.; Tuffour, I.; Quayson, E. E.; Appiah-Opong, R., and Quaye, O. (2018) In Vitro Evaluation of Cytotoxic Activities of Marketed Herbal Products in Ghana. *J of Evidence-Based Integr Med* 23:1-8

Liu, J. and Liu, G. Analysis of Secondary Metabolites from Plant Endophytic Fungi. *Meth in Mol Biol* 2018 1848:25-38. doi: 10.1007/978-1-4939-8724-5_3.

Majekodunmi, S. O.; Adegoke; O. A. and Odekua, O. A. (2008) Formulation of the extract of the stem bark of *Alstonia boonei* as tablet dosage form. *Trop J Pharm Res.* 7(2):987-994

Malan, D. F and Neuba, D. F. R. (2011) Traditional Practices and Medicinal Plant use during Pregnancy by Anyi-Ndenye Women (Eastern Cote d'Ivoire) *Afr J of Rep Health* 15(1)

Melogmo, D. Y.; Lunga, P. K.; Toghueo, K. R. M.; Djague, F.; Dize, D. and Fekam, B. F. (2020). Antibacterial and cytotoxic activities of three medicinal plants from Cameroon (*Alstonia boonei*, *Cassia alata* and *Garcinia lucida*) against diarrhea. *Res. J. Med. Plants* 14:53-63

Nkono Ya Nkono, B. L.; Sokeng, S. D.; Desire, D. D. P. and Kamtchouing, P. (2014) Antihyperglycemic and Antioxydant Properties of *Alstonia boonei* De Wild. (Apocynaceae) Stem Bark Aqueous Extract in Dexamethasone-Induced Hyperglycemic Rats. *Int. J Diab Res.* 3(3):27-35.

Nkono Ya Nkono, B. L.; Sokeng, S. D.; Desire, D. D. P. Frida, L., and Kamtchouing, P. (2015). Subchronic toxicity of aqueous extract of *Alstonia boonei* De Wild. (Apocynaceae) stem bark in normal rats. *Int J of Pharm and Tox. 3*(1), 5-10.

Obame-Engonga, L.; Sima-Obiang, C.; Ngoua-Meye-Misso, R. L.; Orango-Bourdette, J. O., Ndong-Atome, G. R.; Ondo, J. P., and Koudou, J. (2019) In vitro evaluation of the antioxidant and antibacterial activities of *Alstonia boonei* and *Gambeya africana* medicinal plants. *Res J of Life Sci, Bioinform BPCS* 5(5):14-30

Obiagwu, M. O.; Ihekwereme, C. P.; Ajaghaku, D. L. and Okoye, F. B. C. (2014) The Useful Medicinal Properties of the Root-Bark Extract of *Alstonia boonei* (Apocynaceae) May Be Connected to Antioxidant Activity. *Int Scholarly Res Not* 2014:ID 741478

Oguakwa, J. U., (1984) N_{α}-formylechitamidine, an alkaloid from *Alstonia boonei*. *Phytochem* 23(11):2708-2709.

Ogueke, C.; Uwaleke J.; Owuamanam C. I. and Okolue, B. Antimicrobial activities of *Alstonia boonei* stem bark, a Nigerian traditional medicinal plant. *J of Trop Disease* 4 (sup 2):957-962

Ohiagu, F. O.; Chikezie, P. C.; Chikezie, C. M. and Enyoh, C. E. (2021) Anti-cancer activity of Nigerian medicinal plants: A review. *Future J of Pharm Sci* 7:70

Oigiangbe, N.; Tamo, M. and Igbinosa, I. (2013) Bioactivity of *Alstonia boonei* De Wild leaf alkaloid on the growth and development of *Maruca vitrata* Fab. *J of Biopesticides* 6(2):173-177

Oigiangbe, O. N.; Igbinosa, I. B,; Tamo, M. (2007) Insecticidal activity of the medicinal plant, *Alstonia boonei* De Wild, against *Sesamia calamistis J Zhejiang Univ Sci B* 8(10):752-755

Ojewole, J. A. O. (1984) Studies on the pharmacology of echitamine, an alkaloid from the stem bark of *Alstonia boonei* L. (Apocynaceae). *Int J of Crude Drug Res*. 22:121-143.

Ojo, A. O.; Oyinloye, B. E.; Ajiboye, B. O.; Ojo, A. B.; Akintayo, C. O. and Okezie, B. (2014) Dichlorvos induced nephrotoxicity in rat kidney: protective effects of *Alstonia boonei* stem bark extract. *Int J of Pharmacog* 1(7):429-437

Okoye, N. N.; Ajaghaku, D. L.; Okeke, H. N.; Ilodigwe, E. E.; Nworu, C. S. and Okoye, F. B. C. (2014) beta-Amyrin and alpha-amyrin acetate isolated from the stem bark of *Alstonia boonei* display profound anti-inflammatory activity. *Pharm Biol* 52(11): 1478-1486

Okoye, N. N. and Okoye, C. O. B. (2016). Antimicrobial and antioxidant flavonoid glycosides from the leaves of *Alstonia boonei* DE WILD. *J of Pharm Res Int* 10(6): 1-9.

Okwu, D. E. and Ighodaro, B. U. (2010) GC-MS Evaluation of Bioactive Compounds and Antibacterial Activity of the Oil Fraction from the Leaves of *Alstonia boonei* De Wild. *Der Pharma Chemica* 2(1): 261-272

Olajide, O. A.; Awe, S. O.; Makinde, J. M.; Ekhelar, A. I.; Olusola, A. Morebise, O. and Okpako, D. T. 2000) Studies on the anti-inflammatory, antipyretic and analgesic properties of *Alstonia boonei* stem bark. *J of Ethnopharmacol*, 71:179-186

Olanlokun, J.O; Bolaji, O.M. and Agbedahunsi, J. M. (2012) Therapeutic effects of various solvent fractions of *Alstonia boonei* (apocynaceae) stem bark on Plasmodium berghei-induced malaria. *Afr J Med Sci* 41:27-33

Olanlokun, O. J.; Oyebode, T. O. and Olorunsogo, O. O. (2017) Effects of Vacuum Liquid Chromatography (Chloroform) Fraction of the Stem Bark of *Alstonia boonei* on Mitochondrial Membrane Permeability Transition Pore. *J Basic Clin Pharm*. 8:221-225.

Olanlokun, J. O. and Olorunsogo, O. O. (2018) Toxicology of solvent extract and fractions of *Alstonia boonei* De Wild stem bark in Rats. *J Herbmed Pharmacol* 7(3):129-135.

Olanlokun, J. O.; Olotu, A. F.; David, O. M.; Idowu,T. O.; Soliman, E. M. and Olorunsogo, O. O. (2019) A novel compound purified from Alstonia *boonei* inhibits Plasmodium falciparum lactate dehydrogenase and plasmepsin II. *J of Biomol Struct and Dynamics* 37(8):2193-2200.

Olanlokun, J. O.; Olotu, F. A.; Idowu, O. T.; Agoni, C. David, M. O.; Soliman, M. and Olorunsogo, O. O. (2020) In vitro, in silico studies of newly isolated tetrahydro-4-(7-hydroxy-10-methoxy-6, 14-dimethyl-15-m-tolylpentadec-13-enyl) pyran-2-one and isobutyryl acetate compounds from *Alstonia boonei* stem bark. *J of Mol Struct*, 1216, 2020:128225

Olanlokun, J. O.; Olowofolahan, A. O.; Bodede, O.; Adegbuyi, A.T.; Prinsloo, G.; Steenkamp, P. and Olorunsogo, O. O. (2021) Anti-Inflammatory Potentials of the n-Hexane Fraction of *Alstonia boonei* Stem Bark in Lipopolysaccharide-Induced Inflammation in Wistar Rats. *J of Inflam Res* 14:3905-3920

Omoregie, E.S.; Oriakhi, K.; Oikeh, E.I.; Okugbo, O.T. and Akpobire, D. (2014) Comparative Study of Phenolic Content and Antioxidant Activity of Leaf Extracts of *Alstonia boonei* and *Eupatorium odoratum Nig. J. Basic Appl. Sci.* 22(3):91-97

Omoya, F. and Oyebola, T. F. (2019) Antiplasmodial activity of stem bark and leaves of *Alstonia boonei* De Wild. *J of Microbiol and Exper.* 7(5):241–245.

Omoya, F.; Oladipupo, K.; Abe, A. and Udensi, O. (2012) Bioactivity, Qualitative and Quantitative Components of *Alstonia Boonei* Leaf Extracts on Anopheles Mosquito Larvae in Nigeria. *J of Med and Bioengineerig* 1(1):39-41

Opoku, F. and Akoto, O. (2014) Antimicrobial and Phytochemical Properties of *Alstonia boonei* Extracts. *Organic Chem Curr Res* 4(1):1000137

Osadebe, P. 0. (2002). An investigation into the anti-inflammatory properties of the root bark of *Alstonia boonei* bark. *Nig. J Nat. Prod. Med.* 6:39-41

Osadebe, P. (2003) Analgesic properties of alcoholic extract of the root bark of *Alstonia boonei* De Wild. *Nig J of Neuroscience* 6:43-48

Osadolor, H. B.; Ukhureigbe, J. I. and Olaniyan,O. O. (2015) **Antidiabetic and Plasma Endogenous** Antioxidant Activity of *alstonia boonei* in Alloxan-Induced Male Diabetic Rabbits. J. Appl. Sci. Environ. Manage. 19(4):597-601

Osuntokun, O. T. and Ajiga, P. J. (2020) Toxicological Assessment of Synergistic Efficacy of *Alstonia boonei & Capacium frutescens* Extract on *Plasmodium berghei* (NK 65)/*Salmonella typhi* (ATCC 35723) Infected Swiss Albino Mice. *Annals of Pharmacol and Pharmaceutics* 5(4):1187.

Otu, E (2018) Geographical access to Healthcare services in Nigeria- A Review. *Int. J. of Integr Hum.* 10 (1):1-26

Otuu, C. A.; Obiezue, R. N. N.; Okoye, C. I.; Omalu, I. C. J.; Otuu, A. Q. A.; Eke, S. S.; Udeh, E. O.; Ekuma, I. C.; Yamman, H. U.; and Okafor, F. C. (2020). Antimalarial Activity, Phytochemical Composition and Acute Toxicity Tests of Ethanolic Stem Bark Extract of Alstonia boonei De Wild. *Int J of Pathogen Res*, *5*(4):55-63.

Owolabi, O. J.; Arhewoh, I. M.; Innih, S. O.; Anaka, O. N and Monyei, C. F. (2014). The Ethanol Leaf Extract of *Alstonia boonei* (Apocynaceae) Reduces Hyperglycemia in Alloxan-Induced Diabetic Rats. *Nig J of Pharml Sci* 13(1):12 -21.

Oze, G.; Nwanjo, H. and Onyeze, G. (2007) Nephrotoxicity Caused by the Extract of *Alstonia boonei* (De Wild) Stem Bark in Guinea Pigs. *The Internet J of Nutr and Wellness.* 3(2)

Rasoaaivo, P. R.; Wilcox, M.; Gilbert, B. and Wright, C. W. (2011) Whole Plant Extracts versus Single Compounds for the Treatment of Malaria: Synergy and Positive Interactions *Malaria Journal* 10 Suppl 1(Suppl 1):S4

Tolulope, R. A.; Adeyemi, A. I,; Erute, M. A. and Abiodun, T. S. (2015) Isolation and screening of endophytic fungi from three plants used in traditional medicine in Nigeria for antimicrobial activity. *Int J Green Pharm* 9:58-62.

Turkson, B. K; Aboagye, A.; Kofi, P. O.; Mensah, T.; Emmanuel, A.; Yvonne Woyome,Y. and Turkson, A. Y. (2019) A retrospective clinical study of the safety and efficacy of AFA mixture (An herbal antihypertensive product). *J of Herbal Drugs* 9(3):161-164

Uzor, P.; Osadebe, P.; Ozumba, B.; Okafor, S.; Eze, F.; Odoh, U.; Onuoha, J.; (2017) Oxytocic Effect of Extracts and Fractions of *Alstonia boonei* Stem Bark. Paper presented at the 65th International Conference of the Society for Medicinal Plants and Natural Product Research. Sept 3-7, Basel, Switzerland.

WHO (2021) Antimicrobial resistance https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance