

Review Article

Alchornea floribunda (Müll. Arg.) - A review of its phytochemistry and biological activities

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Abstract

Alchornea floribunda is an evergreen plant that grows up to 32 feet tall and belongs to the family of Euphorbiaceae. It is found mainly in African forest undergrowth. In Nigeria, its leaves, stems and roots are widely used in folkloric medicine to manage ailments and diseases. The pharmacological activity of *A. floribunda* depends mainly on the part used. A previous study showed that the leaves have anti-inflammatory, antimicrobial, antioxidant and anti-cancer activities, while its roots and stem possess antibacterial activity. Thus, this review takes a critical look at previously reported findings and information about the phytochemistry, biological activities and various isolated bioactive constituents from the leaf, root and stem of *Alchornea floribunda*.

Keywords: *Alchornea floribunda*, Phytochemistry, Inflammatory, Antimicrobial, Antioxidant, Anti-cancer

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INTRODUCTION

Alchornea floribunda is a shrub commonly found in African forest and is a member of the Euphorbiaceae family. *Alchornea* has many other species including *Alchornea coelophylla*, *Alchornea cordifolia*, *Alchornea hirtella*, and among others [1]. *Alchornea floribunda* leaves, stems and roots are used in Nigerian *trado-medical* practice for the treatment of many ailments including eczema, hepatitis, pains, infectious diseases and inflammatory disorders [2-4]. The water extract of the leaf and root bark is used in the management of human African trypanosomiasis (HATs) in Congo, while the decoction from the leaf is used in Cameroon for

the management of parasitic and bacterial infections [5,6].

Alchornea floribunda is used in folkloric medicine for the management of various ailments and contains anti-inflammatory, antioxidant, antimicrobial, anti-cancer properties and as an aphrodisiac agent [2,7-10]. *Alchornea floribunda* from tropical Africa is reputed to have hallucinogenic properties [11]. The powdered leaves decoction of *A. floribunda* when given to dogs increased its sensitivity of the sympathetic nervous system to epinephrine [12]. *Alchornea floribunda* leaves are eaten in the Congo as an antidote for poison, and the root sap or leaf is administered as a salve to irritated or wounded

skin [13].

The Bwiti tribe in Gabon macerate the roots cortex in palm wine for several days and used as aphrodisiac. The powdered root bark is mixed with food and consumed before a ritual or battle as source of strength [14]. Various *Alchornea* species have been reported to exhibit similar pharmacological activities including antioxidant, hepatoprotective, anti-inflammatory, antiplasmodial, antidiarrhoeal, antimicrobial and as an immunomodulatory [15-25].

Phytochemistry

Several phytochemical analyses of different extracts of *A. floribunda* leaves, stem and roots have been carried out, and the extracts have been shown to contain a wide range of phytochemicals and compounds. Solvent extracts (*n*-hexane and methanol) and column fractions (chloroform and ethyl acetate) of the leaves of *A. floribunda* were found to contain terpenes, sterols, flavonoids, tannins, carbohydrate, glycoside, saponins and alkaloids [26].

Voukeng and co-workers [27] previously reported the phytochemical constituents of the stem bark and leaves of methanol extracts. The leaf extract contained triterpenes, sterols and saponins while the stem bark had alkaloids, triterpenes, polyphenols and saponins. The phytochemical analysis of the solvent fractions (ethyl acetate and *n*-hexane) from the methanol extract of the leaves indicated that steroids and terpenoids were present in the *n*-hexane fraction while saponins, tannins and flavonoids were found in the ethyl acetate fraction [2]. Bio-assay guided purification of the ethyl acetate fraction of the methanol leaves extract by Okoye and Osadebe yielded a novel flavonoidal glycoside 3, 5, 7, 3'-tetrahydroxyflavone-3-O- α -L-rhamnoside [28]. Gas Chromatography–Mass Spectrometric analysis of the analysis of the non-polar fraction (*n*-hexane fraction) of the *Alchornea floribunda* leaves extract revealed the presence of unsaturated and saturated fatty acids and fatty acid esters [19]. Furthermore, the purification of the ethyl acetate sub-fraction of the methanol leaf extract using semi-preparative reverse phase HPLC yielded seven known flavonoid glycosides [29].

Phytochemical investigation of the methanol stem barks and roots extracts led to the isolation of yohmbine alkaloid and three imidazopyrimidine alkaloids [30-32]. Several

studies have been conducted with a view to isolating and characterising the bioactive secondary metabolites of the leaves, roots and stems of *A. floribunda*. These metabolites included steroids, flavonoids and alkaloids (Table 1; Figure 1).

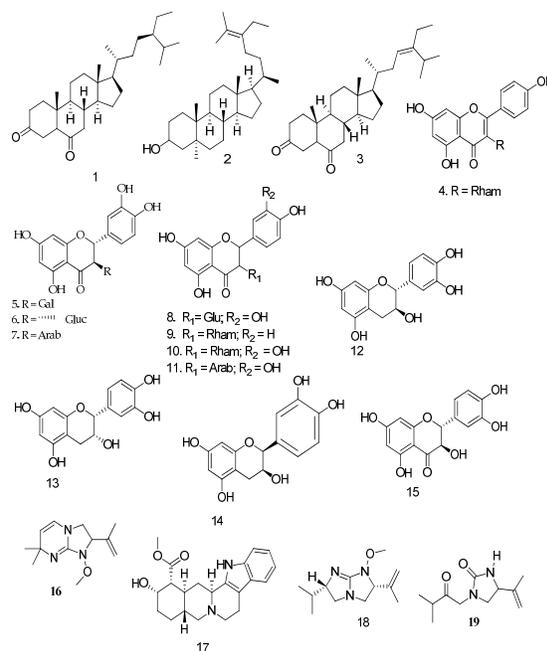


Figure 1: Chemical structure of bioactive compounds isolated from the leaves (1-15), stem bark (16) and roots (17-19) of *A. floribunda*

Biological properties

In the continual search for new drugs, natural products have been found to be superior to combinatorial chemistry for the discovery of novel drug 'lead' compounds that could be developed into new products [33]. Plant extracts, fractions and pure compounds remain a starting point for the discovery of bioactive compounds for combating numerous diseases affecting animals and human beings [34]. *Alchornea floribunda* possesses immunomodulatory, anti-inflammatory, antibacterial and antioxidant activities. Acute toxicity study of the extract was determined using Lorke's method by administering graded doses of methanol leaves extract *in vivo* and the animals were observed for any sign of toxicity and death for 24 h and 14 days respectively [2,4]. The result showed that the extract had a safety margin below 2000 mg/kg (p.o.) and 567.70 mg/kg (i.p.). Lower dose of the extract of *A. floribunda* is recommended for *in vivo* assays.

Table 1: Bioactive compounds isolated from *A. floribunda*

Plant Part	Compound	Code	Class	Biological activity	Reference
Leaves	5 α -stigmastane-3,6-dione	1	Steroid	Anti-inflammatory	8
	3 β -hydroxy-5 α -stigmastane-24-ene	2	Steroid	Anti-inflammatory	8
	5 α -stigmastane-23-ene-3,6-dione	3	Steroid	Anti-inflammatory	8
	Kaempferol-3-O- α -L-rhamnopyranoside	4	Flavonoid	Anti-inflammatory	28
	2R,3R-dihydroquercetin-3-O- β -D-galactopyranoside	5	Flavonoid	Immunomodulatory	29
	2R,3S-dihydroquercetin-3-O- β -D-glucopyranoside	6	Flavonoid	Immunomodulatory	29
	2R,3R-dihydroquercetin-3-O- α -L-arabinopyranoside	7	Flavonoid	Immunomodulatory	29
	2R,3R-dihydroquercetin-3-O- α -L-arabinopyranoside	8	Flavonoid	Immunomodulatory	29
	Quercetin-3-O- β -D-glucopyranoside	9	Flavonoid	Immunomodulatory	29
	Quercetin-3-O- α -L-rhamnopyranoside	10	Flavonoid	Immunomodulatory	29
	Quercetin-3-O- β -D-arabinopyranoside	11	Flavonoid	Immunomodulatory	29
	(-) Catechin	12	Flavonoid	Anti-inflammatory	4
	(-) Epicatechin	13	Flavonoid	Anti-inflammatory	4
	(+) Epicatechin	14	Flavonoid	Anti-inflammatory	4
	(+) Taxifolin	15	Flavonoid	Anti-inflammatory	4
Stem bark	Alchorneine	16	Alkaloid		31, 32
Roots	Yohimbine	17	Alkaloid		30
	Isoalchorneine	18	Alkaloid		32
	Alchorneinone	19	Alkaloid		32

Anti-inflammatory activity

Inflammatory diseases result from the response of the body to injury or infection and is characterized by oedema, redness, pain, and disturbed physiological functions [35-36]. Inflammation is triggered by a lot of chemical mediators including basophils, mast cells, neutrophils, platelets, lymphocytes and macrophages [37-39]. Folkloric uses of the various parts of *A. floribunda* (leaves, stems and roots) in the management of inflammatory disorders have been reported [40].

An *in-vivo* acute and chronic inflammation study on the methanol extract and solvent fractions of the leaves of *A. floribunda* using animal model has been reported [2]. The administration of 200 mg/kg dose of the extract showed moderate inhibition of egg albumen induced oedema (54.69 %) 4 h post-administration of the extract compared to 53.13 % of the control (aspirin).

The ethyl acetate (EF) and *n*-hexane (HF) solvent fractions at a dose of 200 mg/kg elicited a stronger inhibition of oedema (67.19 and 81.25 %, respectively) 4 h post-administrations compared to 53.13 % inhibition for aspirin (100 mg/kg) as a standard drug. In the chronic anti-

inflammatory study, solvent fractions reduced formaldehyde induced arthritis in rats. The result showed that HE (200 mg/kg) showed 36.79 % significant inhibition of leucocytes migration *in vivo* but could not stabilise hypotonicity and heat lysis of human erythrocyte (200 and 400 μ g/mL) *in vitro*. This suggested that the anti-inflammatory properties of the extract and solvent fractions is attributed to the presence of secondary metabolites like terpenoids and steroids in *n*-hexane fraction; flavonoids, tannins and saponins in ethyl acetate fraction [2].

Membrane stabilizing activity is a method of determining the preliminary *in vitro* anti-inflammatory activities of plant extracts, fractions or isolated compounds [41,42]. Inflammation results from the release of lysosomal constituents because of degranulation of their cell membranes. The released lysosomes cause cell death. Stabilization of the membranes will inhibit the release of lysosomes and, thus, offers a mechanism for anti-inflammatory activity.

Stigmastane steroids (**1-3**) obtained from the *n*-hexane leaves extract were assayed *in vivo* and *in vitro* for their anti-inflammatory activity. The compounds at a dose of 20 mg/kg (i.p.) showed significant inhibition of the egg albumen-induced

acute inflammation with **1** having higher inhibition unlike **2** and **3** (50.9, 34.4 and 32.2% respectively) comparable to the inhibition of the standard drugs, indomethacin (39.90%) and prednisolone (48.0%) at a dose of 20 mg/kg 3 h post administration of the compounds and the drugs [8]. Similarly, the compounds at doses of 50 and 100 µg/ear exhibited significant inhibition of xylene-induced oedema which is dose dependent, 2 h post administration. The results showed that the isolated compounds showed better inhibition of the ear oedema than the standard drugs with compounds **1** and **2** at 100 mg/kg having three- or four-times inhibition than the drugs.

Steroids are more lipophilic than indomethacin and prednisolone and penetrate the skin lipoidal layers easily. This accounts for the increased topical anti-inflammatory activity of the compounds *viz-a-viz* the drugs. The *in-vitro* anti-inflammatory study of compounds **1-3** showed significant inhibition of the heat-induced lysis of the human red blood cells which increased with increase in the dose administered, but none of the compounds had effect on hypotonicity-induced lysis. It has been reported that steroids exert their anti-inflammatory activity by their actions on the lysosomal membrane, which is like the human red blood cells [43]. Activity-guided purification of the ethyl acetate fraction of the methanol leaves extract yielded a new favonol glycoside (**4**).

The *in vivo* anti-inflammatory activities of two major ethyl acetate column fractions (EFA and EFB) and the isolated compound were investigated using egg albumen induced rat paw oedema. The column fractions (EFA, 100 mg/kg) exhibited a pronounced and significant inhibition of oedema with inhibition of 78.4% 3 h post administration unlike EFB (100 mg/kg) that exhibited moderate inhibition of oedema (40.5%, 3 h). Compound **4** exhibited a dose dependent inhibition of acute inflammation in a dose dependent manner, with 50 mg/kg (%inhibition = 51.4) having higher inhibition than the standard drug (aspirin, 100 mg/kg; %inhibition = 45.9) 3 h post administration [2].

Immunomodulatory activity

The immune system is the body's natural guard against foreign agents and protects it against a wide variety of pathogens [44]. A healthy and efficient immune system is needed to fight the emergence of dreaded diseases like AIDs and Ebola virus that reduce the immune responses. Study has shown that extracts or fractions from *A. floribunda* are used in the treatment of

immuno-inflammatory diseases [45]. In an *in vitro* assay, flavonoid glycosides (**5-11**) isolated from the leaves of *Alchornea floribunda* were assayed for their immune regulatory activities in relation to the expression of type-1 cytokines (IFN γ and IL-2) by CD4⁺ and CD8⁺T cells using flow cytometric method. These compounds demonstrated their ability to modulate the intracellular expression of IFN γ and IL-2 in culture of splenic T lymphocytes stimulated with and without these compounds in the presence of 2 µM monensin. FACS data analysis of the result showed that stimulation with the compounds (6.25-25 mg/mL) increased the level of CD8⁺/IFN γ ⁺ and CD4⁺/IFN γ ⁺T compared to the untreated cells in the controls. The result showed increase in the ratio of CD8⁺ and IFN γ ⁺ from 57.85 to 72.45% compared to 57.85% for the untreated control. Also, the ratio of CD4⁺ and IFN γ ⁺T increased from 3.21 to 7.21% compared to 2.57% for the untreated control with no secretion of intracellular IL-2 by treated T cells [29].

Antioxidant activity

Free radicals have been implicated in many diseases due to cellular damage caused by free radicals *in vivo*. Oxidative stress is responsible for many degenerative diseases like cancer, heart disease, aging, diabetics and immune system disorder [46]. Plant polyphenols have been reported to have good radical scavenging ability [47,48]. The *in vitro* antioxidant activity of compounds **12-15** isolated from the purification of the ethyl acetate sub-fraction of the methanol leaves extract was investigated. *In vitro* antioxidant assay was determined using 2, 2-diphenyl-1-picrylhydrazyl (DPPH), ferric reducing antioxidant power (FRAP) and hydrogen peroxide scavenging activity assays. The compounds showed significant *in vitro* antioxidant effect (EC₅₀ = 88–19 µg/mL) relative to the positive control (ascorbic acid, EC₅₀ = 6 µg/mL) in the DPPH model; EC₅₀ value range of 88–48 µg/mL compared to 66 µg/mL of the positive control in FRAP model and EC₅₀ of 18–8 µg/mL compared to the control (8 µg/mL) in H₂O₂ assay.

Compound **14** had the highest radical scavenging activity in the DPPH and H₂O₂ models but had no antioxidant effect in the FRAP assay [4]. The *in vivo* antioxidant assay of the methanol extract and solvent fractions was investigated by determining their effects on serum catalase enzyme, serum superoxide dismutase enzyme and serum malondialdehyde in experimental animals. Ethyl acetate fraction (200 mg/kg) significantly elevated the level of

catalase enzyme activity with a significant reduction in the level of serum malondialdehyde. Administration of 200 and 400 mg/kg doses of ethyl acetate fraction caused a significant increase in the serum superoxide dismutase and catalase enzyme, but only 400 mg/kg dose caused an increase in serum superoxide dismutase enzyme unlike the *n*-butanol fraction that significantly caused an increase in both enzymes.

Antibacterial/antimicrobial activity

The demand for new anti-infectious drugs, especially those with activity against Gram negative and recalcitrant bacteria, is urgent [49]. More than thirteen million lives across the globe are lost each year due to infectious diseases [50]. Over the last ten years, this figure has doubled resulting from the emergence of multi-drug-resistant strains. Regrettably, only few new antibiotics have been introduced to the market in the last four decades. The Global cost of antimicrobial resistance to GDP is estimated to be between \$ 2.1 trillion - \$ 124.5 trillion dollars [51]. Natural products made by plants and microorganisms represent an unparalleled starting point for the treatment of infectious disease [52].

Okoye and Ebi [26] have reported wide range of data on the antibacterial and antifungal activities of leaves extracts and solvent fractions of *Alchornea floribunda* using the agar well diffusion method against *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Salmonella keitambii*, *Aspergillus niger* and *Candida albicans*. The result showed that only fraction A2 (terpenoid rich fraction) obtained from the purification of the *n*-hexane extract showed pronounced antimicrobial activity with inhibition zone diameters (IZD) of 42, 34 and 32 mm respectively for *Pseudomonas aeruginosa*, *Salmonella keitambii* and *Bacillus subtilis* respectively compared to ciprofloxacin (drug) with IZD of 45, 56 and 40 mm against *P. aeruginosa*, *S. keitambii* and *B. subtilis* respectively. Purification of the terpenoid-rich fraction (A2) yielded 14 sub-fractions, with only four sub-fractions (AF7, AF9, AF12 and AF13) having weak antimicrobial activities against *S. keitambii* and *P. aeruginosa* (IZD value range: 13-18 mm). The antibacterial activities of aqueous, methanol, ethanol, ethyl acetate, chloroform and *n*-hexane extracts of the leaves, stems and roots of *A. floribunda* using the micro-dilution assay have been reported [3]. The extracts were tested against Gram-positive bacterial, like *Staphylococcus saprophyticus*

ATCC 15305, *Staphylococcus aureus* ATCC 25923, *Bacillus cereus* ATCC 11778 and *Enterococcus faecalis* ATCC 29212 and, as well as Gram-negative strains such *Klebsiella pneumoniae* ATCC 13883, *Moraxella catarrhalis* ATCC 23246, *Escherichia coli* ATCC 25922, and *Proteus mirabilis* ATCC 43071.

The result showed that extracts from the moderately polar solvents (chloroform, ethyl acetate, methanol and ethanol) had the highest activities (MIC range: 50-1000 $\mu\text{g/mL}$) than extracts from the non-polar (*n*-hexane) and aqueous solvents (MIC range: 130-1000 $\mu\text{g/mL}$), with the leaves extracts having higher antibacterial activity against the six tested organisms. The ethanol leaf extract had minimum inhibitory concentration (MIC) of 50 $\mu\text{g/mL}$ for *Staphylococcus aureus* and 63 $\mu\text{g/mL}$, for *Staphylococcus saprophyticus* and *Klebsiella pneumoniae*. However, the methanol leaf extract had MIC of 70 $\mu\text{g/mL}$ for *Bacillus cereus*, and *Escherichia coli* and 63 $\mu\text{g/mL}$ for *Staphylococcus saprophyticus*, *Klebsiella pneumoniae*. Chloroform and ethyl acetate roots extracts showed pronounced activity against *Staphylococcus aureus* (MIC = 50 $\mu\text{g/mL}$) with the ethyl acetate stems extracts showing improved activity against *Staphylococcus saprophyticus* and *Klebsiella pneumoniae* with MIC value of 63 $\mu\text{g/mL}$.

The antibacterial activity of some medicinal plants of Cameroonian origin against thirty-six multidrug resistant (MDR) bacteria phenotypes using broth micro-dilution method has been reported [27]. The result showed that the methanol leaves and stem-bark extracts of *A. floribunda* inhibited the growth of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Enterobacter aerogenes*, and *Providencia stuartii* strains with MIC value range of 128–1024 $\mu\text{g/mL}$. Methanol leaves extract exhibited pronounced activity against *S. aureus* ATCC 25923 and *S. aureus* MRSA6 with MIC values of 128 $\mu\text{g/mL}$. This agrees with the results obtained by Noundou et al [3] who got similar result against *S. aureus* ATCC 25923 (MIC = 130 $\mu\text{g/mL}$). Plant extracts are considered to exhibit antibacterial activity if their MIC values got from *in vitro* assay are in the range of 100–1000 $\mu\text{g/mL}$ [53].

Anti-trypanosomal and anti-malaria activities

Human African trypanosomiasis (HATs) is a disease caused by protozoan *Trypanosoma*; and transmitted to humans through the bite of Tsetse flies. It ranks high in the list of neglected tropical diseases (NTDs) and causes considerable

morbidity and mortality in livestock [54,55]. Malaria is also a protozoan disease caused by *Plasmodium* and transmitted to humans via the bite of the female Anopheles mosquito. It is the leading cause of child deaths in Nigeria and West Africa. Over 192,284 deaths resulting from malaria were recorded in 2015 [56]. Conventional drugs for the treatment of these parasitic diseases have some adverse effects and the search for new anti-protozoan agents is urgent [57]. Musuyu Muganza et al [58] have demonstrated that the aqueous roots and leaves extracts of *A. floribunda* have both anti-trypansomal and anti-malaria activities in an *in vivo* study. Their findings showed that the extracts could clear the parasitaemia levels of *T. cruzi*, *T. brucei brucei*, and *L. infantum* with IC₅₀ values of 37.26, 19.65, and > 64 µg/mL respectively. The extracts also exhibited remarkable activity against K1 strain of *P. falciparum* (K1 strain) with IC₅₀ value of 20.80 µg/mL.

CONCLUDING REMARKS

This review of *A. floribunda* reveals that various parts of the plant have different biological activities. The phytochemical constituents depend on the part of the plant investigated. While alkaloids are present in the stem-bark and roots, flavonoids and terpenoids are predominant in the leaves. These secondary metabolites exhibit anti-inflammatory, antioxidant, immunomodulatory, antimicrobial and anti-protozoan activities.

DECLARATIONS

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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