Abstract: *Alchornea floribunda* is a small evergreen plant that grows up to 32 feet tall. It belongs to the family of Euphorbiaceae and is found mainly in African forest undergrowth. In Nigeria its leaves, stems and roots are widely used in folkloric medicine in the management of many ailments and diseases. The pharmacological activity of *A. floribunda* depends mainly on the part used. The leaves have been documented to possess anti-inflammatory, antimicrobial, antioxidant and anti-cancer activities while the roots and stems have been reported to possess antibacterial activity. Thus, this review summarizes all the findings and information about the phytochemistry, biological activities and various isolated bioactive constituents from the leaves, roots and stems of *Alchornea floribunda*.

Keywords: Anti-inflammatory Activity, Immunomodulatory Activity, Antioxidant Activity, Antimicrobial activity, Anti-protozoan activities.

1. Introduction

*Alchornea floribunda* (*A. floribunda*) is a shrub which is widely distributed in African forest and is a member of the Euphorbiaceae family. *Alchornea* has many other species including *Alchornea coelophylla*, *Alchornea cordifolia*, *Alcornea hirtella*, and among others [1]. *A. floribunda* leaves, stems and roots are used in Nigeria 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 leaf decoction is used in Cameroon for the treatment of parasitic and bacterial infections [5, 6]. *Alchornea floribunda* possess wide range of use in folkloric medicine and is thus used in the treatment of various ailments including been used as anti-inflammatory, antioxidant, antimicrobial, anti-cancer and as an aphrodisiac agent [2, 7-10]. *A. floribunda* from tropical Africa is reputed to have hallucinogenic properties [11]. When a decoction of powdered leaves of *A. floribunda* was administered to dogs, it increased the sensitivity of the sympathetic nervous system to epinephrine [12]. The leaves of *A. floribunda* are eaten in the Congo as an antidote for poison, and the leaf or root sap is applied to irritated or wounded skin as a salve [13]. The Bwiti tribe in Gabon macerate the roots cortex in palm wine for several days and used as aphrodisiac. The root bark may be sun-dried and powdered, then mixed with food and consumed prior to a ritual or a battle to give strength [14]. Various *Alchornea* species have been reported to exhibit similar pharmacological activities including been used as antioxidant, hepatoprotective agent, anti-inflammatory, antiplasmodial, antidiarrheal, antimicrobial and as an immunomodulator [15-25].
2. Phytochemistry

Several phytochemical analysis 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] have reported the phytochemical constituents of the leaves and stem bark methanol extracts. The leave extract contained triterpenes, sterols and saponins while the stem bark had alkaloids, triterpenes, polyphenols and saponins. The phytochemical analysis of the solvent fractions (*n*-hexane and ethyl acetate) of the methanol leaves extract showed that terpenoids and steroids were present in the *n*-hexane fraction while flavonoids, tannins and saponins were present in ethyl acetate fraction [2]. Bioactivity guided purification of the ethyl acetate fraction obtained from the methanol leaves extract by Okoye and Osadebe led to the isolation of a novel flavonoidal glycoside 3,5,7,3’-tetrahydroxyflavone-3-O-α-L-rhamnoside [8]. Analysis of the lipophilic fraction (*n*-hexane fraction) of the *Alchornea floribunda* leaves extract using GC–MS apparatus revealed presence of saturated and unsaturated long chain fatty acids and fatty acid esters [19]. Semi-preparative reverse phase HPLC purification of the ethyl acetate fraction of the methanol leaves extract yielded seven known flavonoid glycosides [28]. Phytochemical investigation of the methanol stem bark and roots extracts led to the isolation of yohimbine alkaloid and three imidazopyrimidine alkaloids [29-31]. Several studies have been conducted with a view to isolating and characterising the bioactive secondary metabolites from the leaves, roots and stems of *A. floribunda*. These metabolites included steroids, flavonoids and alkaloids (Table 1; Figure 1).

3. Biological Activities

In the continual search for new drugs, natural products have been found to be superior to combinatorial chemistry for discovering of novel drug ‘lead’ compounds that could be developed into new products [32]. 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 [33]. *A. floribunda* has been reported to possess anti-inflammatory, immunomodulatory, antibacterial and antioxidant activities. To determine the safe dose of the extract, acute toxicity study using Lorke’s method was conducted by administering graded doses of methanol leaves extract in vivo and the animals were observed for signs of toxicity and mortality 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.), thus lower dose of the extract of *A. floribunda* is recommended for an in vivo assay.

3.1. Anti-inflammatory Activity

Inflammatory diseases result from the body response to injury or infection and is characterized by oedema, redness pain, and disturbed physiological functions [34, 35]. Inflammation is triggered by a lot of chemical mediators including basophils, mast cells, neutrophils, platelets, lymphocytes and macrophages [36-38]. Folkloric uses of the various parts of *A. floribunda* (leaves, stems and roots) in the management of inflammatory disorders has been reported [39]. An in-vivo acute and chronic inflammation study on the methanol extract and solvent fractions of the leaves of *A. floribunda* in animal model has been reported [2]. The extract at a dose of 200 mg/kg 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 *n*-hexane (HE) and ethyl acetate (EF) solvent fractions at a dose of 200 mg/kg showed a higher percentage inhibition of oedema (81.25 and 67.19%) respectively 4 h post administration.
administration 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 μg/mL) in vitro. This study suggested that the anti-inflammatory properties of the extract and solvent fractions could be attributed to the 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 [40, 41]. 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) isolated from the n-hexane leaves extract were investigated for their in vivo and in vitro anti-inflammatory activity. The result showed that 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 evoked significant inhibition of xylene-induced oedema in a dose dependent manner, 2 h post administration. The result 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 penetrates the skin lipidal layers easily. This could account for the higher topical anti-inflammatory activity of the compounds compared to the drugs. In the in-vitro anti-inflammatory study, compounds 1-3 significant inhibited heat-induced lysis of the human red blood cells in a dose dependent manner, 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 [42]. Bioassay-guided purification of the ethyl acetate fraction of the methanol leaves extract led to the isolation of a new favonol glycoside (4). The in vivo ant-inflammatory activities of two major ethyl acetate column fractions (EFA and EFB) including 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].

3.2. Immunomodulatory Activity

The body’s immune system is its natural guard against foreign agents and is composed of a system of biological structures and processes that protect against a wide variety of pathogens [43]. A healthy and efficient immune system is thus, 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 obtained from A. floribunda have both activity and therapeutic uses on immuno-inflammatory diseases [44]. In an in vitro assay, flavonoid glycosides (5-11) isolated from the leaves of Alchornea floribunda were investigated for their immune regulatory activities in relation to the expression of type-1 cytokines (IFNγ and IL-2) by CD4+ and CD8+ T cells using flow cytometric method. The compounds demonstrated their ability to modulate the intracellular expression of IFNγ and IL-2
in culture of splenic T lymphocytes stimulated with and without these compounds in presence of 2 μM monensin. The result of FACS data analysis showed that simulation with the compounds (6.25-25 mg/mL) increased the level of CD8+/IFNγ+ and CD4+/IFNγ+ T compared to the cells found in untreated controls. The ratio of CD8+ and IFNγ+ increased from 57.85 to 72.45% compared to 57.85% for the untreated control; while the ratio of CD4+ and IFNγ+ T increased from 3.21 to 7.21% compared to 2.57% for the untreated control. Also, there was no secretion of intracellular IL-2 by treated T cells, and thus this was not detected [45].

3.3. 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 ethyl acetate fraction of the methanol leaves extract was investigated. The in vitro antioxidant assay was achieved using 2,2-diphenyl-1-picrylhydrazyl (DPPH), ferric reducing antioxidant power (FRAP) and hydrogen peroxide scavenging activity assays. The tested compounds showed significant in vitro antioxidant effect (EC50 = 88–19 μg/mL) compared to the positive control (ascorbic acid, EC50 = 6 μg/mL) in the DPPH model; while the compounds had 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 8 μg/mL for the control 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 at a dose of 200 mg/kg significantly elevated the level of catalase enzyme activity with a significant reduction in the level of serum malondialdehyde. Also, the ethyl acetate fraction (200 and 400 mg/kg) caused a significant increase in the serum superoxide dismutase and catalase enzyme, but only 400 mg/kg dose caused an in increase in serum superoxide dismutase enzyme unlike the n-butanol fraction that significantly caused an increase in both enzymes.

3.4. Antibacterial/antimicrobial Activity

The quest for new antibacterial, especially those with activity against Gram negative and recalcitrant bacteria, is urgent [49]. Over 13 million lives worldwide are currently claimed each year due to infectious diseases [50]. Over the last decade this figure has doubled due to the emergence of multi drug resistant strains. Conversely very few new antibiotics have been introduced to the market in the last 40 years. The Global cost of antimicrobial resistance to GDP is calculated as 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 antimicrobial activities of leaves extracts and solvent fractions of Alchornea floribunda using the agar well diffusion method against Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa, Salmonella keitambii, Candida albican and Aspergillus niger. 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. Further purification of the terpenoid rich fraction (A2) yielded 14 sub-fractions, with only four sub-fractions (AF7, AF9, AF12 and AF13) having weak antimicrobial activity.
against P. aeruginosa and S. keitambii (IZD value range: 13-18 mm). Noundou et al. [3] reported a study of the antibacterial activities of n-hexane, chloroform, ethyl acetate, ethanol, methanol and water roots, stems and leaves extract of A. floribunda using the micro-dilution assay. The extracts were tested against Gram-positive bacteria, like Bacillus cereus ATCC 11778, Enterococcus faecalis ATCC 29212, Staphylococcus aureus ATCC 25923 and Staphylococcus saprophyticus ATCC 15305, as well as Gram-negative strains such Escherichia coli ATCC 25922, Klebsiella pneumoniae ATCC 13883, Moraxella catarrhalis ATCC 23246 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 μg/mL) than extracts from the non-polar (n-hexane) and aqueous solvents (MIC range: 130-1000 μg/mL), with the leaves extracts showing the highest antibacterial activity for six of the tested organisms. The ethanol leaves extract had minimum inhibitory concentration (MIC) of 50 μg/mL for Staphylococcus aureus and 63 μg/mL for Staphylococcus saprophyticus and Klebsiella pneumoniae respectively while the methanol leaves extract had MIC of 70 and 63 μg/mL for Bacillus cereus, Escherichia coli; and Staphylococcus saprophyticus, Klebsiella pneumoniae respectively. The ethyl acetate and chloroform roots extracts showed pronounced activity against Staphylococcus aureus (MIC = 50 μg/mL) with the ethyl acetate stems extracts showing improved activity against Staphylococcus saprophyticus and Klebsiella pneumoniae with MIC value of 63 μg/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, Enterobacter aerogenes, Escherichia coli and Providencia stuartii strains with MIC value range of 128-1024 μg/mL. The methanol leaves extract showed pronounced activity against S. aureus ATCC 25923 and S. aureus MRSA6 with MIC values of 128 μg/mL. This agrees with the results obtained by Noundou et al. [3] who got MIC value of 130 μg/mL against S. aureus ATCC 25923. Study shows that extracts from plants are considered to exhibit antibacterial activity if their MIC values gotten from in vitro assay is in the range of 100-1000 μg/mL [53].

3.5. Anti-trypanosomal and anti-malaria activities

Human African trypanosomiasis (HATs), a disease caused by the parasitic protozoan Trypanosoma; transmitted to humans via the bite of bloodsucking Tsetse flies; ranks high in the list of neglected tropical diseases (NTDs) and causes considerable morbidity and mortality in livestock [54, 55]. Malaria is protozoan disease caused by Plasmodium and transmitted to humans via the bite of the female Anopheles mosquito. Malaria is the leading cause of child deaths in Nigeria and sub-Saharan Africa. In 2015, 192,284 deaths resulting from malaria were recorded [56]. Conventional drugs for the treatment of these parasitic diseases is not safe and thus the search for new anti/protozoan agents, with less adverse effects [57]. Musuyu Muganza et al. [58] has demonstrated that the aqueous roots and leaves extracts of A. floribunda have both anti-trypanosomal 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 with IC50 value of 20.80 μg/mL.
Figure 1. Chemical structure of bioactive compounds isolated from the leaves (1-15), stem bark (16) and roots (17-19) of A. floribunda.
Table 1: Bioactive compounds isolated from *A. floribunda*

<table>
<thead>
<tr>
<th>Plant Part</th>
<th>Compound</th>
<th>Code</th>
<th>Class</th>
<th>Biological activity</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Leaves</td>
<td>5α-stigmastane-3,6-dione</td>
<td>1</td>
<td>Steroid</td>
<td>Anti-inflammatory</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>3β-hydroxy-5α-stigmastane-24-ene</td>
<td>2</td>
<td>Steroid</td>
<td>Anti-inflammatory</td>
<td>8</td>
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<td></td>
<td>5α-stigmastane-23-ene-3,6-dione</td>
<td>3</td>
<td>Steroid</td>
<td>Anti-inflammatory</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Kaempferol-3-O-α-L-rhamnopyranoside</td>
<td>4</td>
<td>Flavonoid</td>
<td>Anti-inflammatory</td>
<td>28</td>
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<tr>
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<td>2R,3R-dihydroquercetin-3-O-β-D-galactopyranoside</td>
<td>5</td>
<td>Flavonoid</td>
<td>Immunomodulatory</td>
<td>29</td>
</tr>
<tr>
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<td>2R,3S-dihydroquercetin-3-O-β-D-glucopyranoside</td>
<td>6</td>
<td>Flavonoid</td>
<td>Immunomodulatory</td>
<td>29</td>
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<td>2R,3R-dihydroquercetin-3-O-α-L-arabinopyranoside</td>
<td>7</td>
<td>Flavonoid</td>
<td>Immunomodulatory</td>
<td>29</td>
</tr>
<tr>
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<td>2R,3R-dihydroquercetin-3-O-α-L-arabinopyranoside</td>
<td>8</td>
<td>Flavonoid</td>
<td>Immunomodulatory</td>
<td>29</td>
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<td></td>
<td>Quercetin-3-O-β-D-glucopyranoside</td>
<td>9</td>
<td>Flavonoid</td>
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<td>29</td>
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<td>10</td>
<td>Flavonoid</td>
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<td>29</td>
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<td>Quercetin-3-O-β-D-arabinopyranoside</td>
<td>11</td>
<td>Flavonoid</td>
<td>Immunomodulatory</td>
<td>29</td>
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<tr>
<td></td>
<td>(-) Catechin</td>
<td>12</td>
<td>Flavonoid</td>
<td>Anti-inflammatory</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>(-) Epicatechin</td>
<td>13</td>
<td>Flavonoid</td>
<td>Anti-inflammatory</td>
<td>4</td>
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<td></td>
<td>(+) Epicatechin</td>
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<td>Flavonoid</td>
<td>Anti-inflammatory</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>(+) Taxifolin</td>
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<td>Flavonoid</td>
<td>Anti-inflammatory</td>
<td>4</td>
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<tr>
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<td>Alkaloid</td>
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</table>

4. Conclusion

The review study of *A. floribunda* revealed that various parts of the plant possess 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 exhibited anti-inflammatory, antioxidant, immunomodulatory, antimicrobial and anti-protozoan activities.

4. Funding

This research received no external funding.

4. Conflicts of Interest

There is no conflict of interest in this research work.
References


