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Review

The Phytochemistry, Ethnobotanical, and Pharmacological Potentials of the Medicinal Plant-*Vernonia amygdalina* L. (bitter Leaf)

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ABSTRACT

Background: *Vernonia amygdalina* is traditionally used to treat a variety of diseases including diarrhoea, fungal and bacterial infections, inflammation, cancer, diabetes, and its squeezed juice can be applied on wounds.
Objective: This study reviewed the phytochemistry, ethnopharmacological, and pharmacological potentials of *V. amygdalina.*
Methods: Literature search of relevant papers (1994-2021) were performed using ScienceDirect, Springer, Wiley and PubMed databases. For this review study, only publications written in English were utilized.
Results: The bioactive compounds extracted from *V. amygdalina* includes 6β,10β,14β trimethylheptadecan-15 α-olyl-15-O-β-D-glucopyranosyl-1,5 β olide, glucuronolactone, 11 α-hydroxyurs-5,12-dien-28-oic acid-3 α,25-olide, 10-geranilanyl-O-β-D-xyloside, 1-heneicosenol O-β-D-glucopyranoside, apigenin, luteolin (3´,4´,5,7tetrahydroxyflavone), vernolide, hydroxyvernolide, 3′-deoxyvernodalol , vernodalol, diterpene (ingenol-3-angelate), vernomygdin, 4-methylumbelliferone, cephantharin, cryptolepine, isocryptolepine, neocryptolepine, courmarins, vernolepin, and vernoniosides. Various *in vivo* and *in vitro* studies revealed that *V. amygdalina* and its bioactive components possess pharmacological activities such as antioxidant, anti-inflammatory, anticancer, antimicrobial, hepatoprotective,antidiarrheal, anti-diabetic, and neuroprotective activities.
Conclusion: This review demonstrated that *V. amygdalina* possess therapeutic effects against a wide variety of diseases. The efficacy of *V. amygdalina* in ameliorating diseases is attributed to its antioxidant activity and ability to improve the antioxidant system. Despite the vast pharmacological activities of *V. amygdalina*, more human clinical trials are needed to identify effective and safe doses for treatment of various diseases.

1. Introduction

Recently, researchers have set out to uncover a new source of medicinal material that is generated naturally and has a less impact on human health, and the aquatic environment. Since organic herbal products are becoming increasingly popular as food supplements across the world, herbal plant-based approach is one of the choices accessible. Herbal medicinal practice makes use of phytochemicals found in plants; therefore, understanding and characterizing phytochemicals found in medicinal plants is critical for effective consumption and conservation (Alabi and Adeyemi, 2021). *V. amygdalina* is mostly cultivated and used in traditional medicinal practices in Africa and Asia's tropical areas. In the pharmacopeia, particularly in African origin, *V. amygdalina* is one of the nutritionally and economically viable plants used for its insect repellent and anti-tumor effects.

Vernonia amygdalina is an angiosperm belonging to the order, Asterales (Toyang and Verpoorte, 2013). The plant belongs to the Asteraceae family, is grouped under the genus *Vernonia*, and species *amygdalina.* The genus is predominantly grown in the tropical regions and possesses several economic importance. The complete name of the plant is *Vernonia amygdalina* Del. (Toyang and Verpoorte, 2013). In Africa, *V. amygdalina* is the common name for this bitter-tasting plant (Abosi and Raseroka, 2003). The plant is predominantly cultivated in the tropical regions of Africa, especially in the West African (Tekou et al., 2018). In Igbo, Yoruba, and Hausa tribes of Nigeria, it is called as "Olugbu", "Ewuro" and "Fetefete" respectively . It is a soft woody shrub that

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Fig. 1. *V. amydalina* L. plant parts. A. Leaves of *V. amydalina* showing its phyllotaxy, B. Leaves with stalk-sourced from bushes located at Amaiyi, Igbere, Autonomous Community, Abia State, Nigeria.

grows perpetually to a height of 1 m to 6 m (IfedibaluChukwu et al., 2020). This shrub can withstand a broad range of weather conditions (Tekou et al., 2018). It is commonly called "bitter leaf" due to its characteristic bitter taste and this may be attributed to its anti-nutritional contents (IfedibaluChukwu et al., 2020)(Fig 1).

V. amygdalina leaves are 6 mm in diameter and 20 cm long (Habtamu and Melaku, 2018), it is dark green and is consumed in a wide variety of delicacies in African countries. *V. amygdalina* leaves are high in nutrients such as vitamins, fibre, carbs, and minerals, making them an important part of the human diet (Oyeyemi et al., 2018). Alara et al. reported some of the phytochemicals including alkaloids, tannins, saponins, flavonoids, polyphenols, alkaloids, anthraquinone, edotides, xanthones, coumarins and sesquiterpenes have been identified in the plant (Alara et al., 2017). These bioactive compounds have been extracted and analyzed using various techniques such as liquid chromatography with tandem mass spectrometry (LC-MS/MS) analysis (Hasibuan et al., 2020), microwave-assisted extraction (MAE) (Alara et al., 2019), soxhlet extraction (Tunasamy et al., 2019). Flavones extracted from flavonoids present in *V. amygdalina* include luteolin, luteolin 7-O-b-glucuronide, and luteolin7-O-b-glucoside (Alabi and Adeyemi, 2021).

The pharmacological significance of *V. amygdalina* is due to the bioactive chemicals isolated from the plant leaves. Cold water extract of *V. amygdalina* has reportedly been used in the suppression of cancer (Yedjou et al., 2018), attenuation of dietary induced obesity (Atangwho et al., 2012), treatment of typhoid (Fadimu *et al.*, 2014), inflammatory diseases (Asante et al., 2019), malaria (Okpe et al., 2016), kidney diseases (Atangwho et al., 2012), and gastrointestinal disorders (Akah and Ekekwe, 1995). They also possess analgesic activity (Njan *et al.*, 2008), neuroprotective effects (Oladele et al., 2020), hepatoprotective effects, antioxidant activity, and anti-allergic activity (Ngatu et al., 2012). Fadimu et al. contended that extracts of *V. amygdalina* could be employed in the treatment of sexually transmitted infections and urinary tract infections (Fadimu et al., 2014). Fevers, coughs, constipation, and hypertension have been successfully treated with tonics derived from extracts of *V. amygdalina* (Amira and Okubadejo, 2007). Michael et al. also opined that *V. amygdalina* extracts could be utilised in the treatment of eczema and maintenance of healthy blood glucose levels (Michael et al., 2010). Although there is limited information as regards to the toxicity of *V. amygdalina*, Njan et al. reported on the toxicity of high dosage of extracts from the leaves (Njan et al., 2008). The aim of this review is to explore the pharmacological potentials of *V. amygdalina* and the extracted phytochemicals therein. This study will also provide relevant information on the beneficial effects of *V. amygdalina* as well as to incite further studies that may recommend the effectiveness and application of the extracts therein in the pharmacopeia and synthesis of new drugs.

2. Methods

All resources used for this review were collected solely from the internet databases Pubmed (https://pubmed.ncbi.nlm.nih.gov/), Springer (https://www.springer.com/gp), ScienceDirect (https://www.sciencedirect.com/) and Wiley (https://www.wiley.com/en-us) from 1994-2021 (accessed 21 May 2021). The electronic online databases were opened. In the search tab, different phrase combinations and truncations of keywords were typed such as "*V. amydalina* and phytochem* OR "*V. amydalina* and ethnopharmac* OR "bitter leaf and pharmac* OR "*V. amydalina* and phytochem* AND "bitter leaf and antioxidant" OR "*V. amydalina* and anticancer", "bitter leaf and anti-diabetic" OR *V. amydalina* and hepatoprotective", "*V. amydalina* and antimicrobial" OR "*V. amydalina* and antibacterial". The title, abstract as well as the effect size of the searched articles were carefully read and reviewed whether they included relevant studies on the phytochemistry, ethnobotanical and pharmacological activities of *V. amydalina*. Only publications written in English were used in this review.

3. Results and Discussion

3.1. Ethnopharmacological uses of V. amygdalina L

V. amygdalina has several medical, industrial, food, and traditional uses. The plant is used as a tonic in the treatment of fever, constipation, and many illnesses in traditional and herbal Nigerian medicine (Howard et al., 2016). Tonics from this medicinal plant are used in the treatment of sexually transmitted diseases. In general, the plant is cultivated to provide a significant source of edible vegetable. The plant is also used in the brewing industry as an alternative to hops in the production of beer. The Congolese maximizes *V. amygdalina*'s medicinal potential by using it to treat cough and haemorrhoids (Ngatu et al., 2012). The leaves are frequently utilized in the treatment of malaria in Ethiopia. Several scientific studies have found that the herb has antioxidative, anti-inflammatory, and anticancer properties (Bihonegn et al., 2019; IfedibaluChukwu et al., 2020).

3.2. Phytochemistry/bioactive compounds of Vernonia amygdalina L

Alabi and Adeyemi (2021) uncovered several flavonoids (luteolin 7-O-b-glucuronide, luteolin 7-O-b-glucoside) in *V. amygdalina* ethanolic preparations. All three flavones have strong antioxidant properties, particularly luteolin (3´,4´,5,7 tetrahydroxyflavone). Other phytochemicals present include alkaloids, anthraquinone, steroid, phenol, phytate, oxalate, cyanogenic glycoside, tannins and saponins. Hasibuan et al. (2020) used LC-MS/MS analysis to investigate the phytochemicals found in *V. amygdalina*. The findings revealed the presence of the following flavonoids: apigetrin, apigenin, luteolin, diosmetin, baicalin, rhoifolin, and scutellarin. Toyang and Werpoorte (2013) examined the isolated phytochemicals obtained from *V. amygdalina* extracts and showed that vernonioside A3, vernodalol, vernolepin, vernodalin, 11,13-dihydrovernodalin, and hydroxyvernolide are among the isolated bioactive chemicals and flavonoids. The reports of Adaramoye et al. (2008a) showed that an increased content of flavonoids such as luteolin-7-O-glucoside in mice treated against liver toxicity might be connected to a reduction in lipid peroxidation (LPO) levels in irradiated animals pretreated with *V. amygdalina* extracts.

Using LC-MS analysis, Erukainure et al. (2018) identified the phytochemicals found in *V. amygdalina*. The study revealed the presence of nicotinic acid, cumidine, and 3-methyl-isoquinoline. *V. amygdalina* alkaloids were discovered and described by Omojokun et al. (2019). The extract of alkaloids was quantified using GC-MS. 1-Hexanamine, dimethylamine, 1-fluorononane, 1,3-cyclooctadiene, and hexadecanamide are

examples of isolated alkaloid compounds. a Iwalokun (2008) identified phytoconstituents with anti-plasmodial action from the extract and quinoline alkaloids such as cephantharin, cryptolepine, isocryptolepine, and neocryptolepine, as well as courmarins and terpenoids, are among these compounds.

IfedibaluChukwu et al. (2020) isolated chemicals from *V. amygdalina* extracts,including vernodalin, vernomygdin, vernoniosides A1, A2, A3, B1, vernoniosides A4, B2, B3, vernoniosides D and E, vernodalol, epivern-odalol, phytol, and 4-methyl-vinyl butyrate, (z,z,z)-methyl ester-9,12,15-octadecatrienoic acid. Several chemicals were isolated from methanolic stem-bark preparations using a chromatographic method including glucuronolactone (CMP3), 10-geranilanyl-O-β-D-xyloside (CMP2), 11 α-hydroxyurs-5,12-dien-28-oic acid-3 α, 25-olide (CMP1), 1-heneicosenol O-β-D-glucopyranoside (CMP4) and 6β,10β,14β-trimethylheptadecan-15 α-olyl-15-O-β-D-glucopyranosyl-1,5 β-olide (CMP5) (Vernoniaolide glucoside) (Table 1).

Hasibuan et al. (2020) used LC-MS/MS analysis to investigate the phytochemicals contained in *V. amygdalina*. The findings revealed the presence of diterpene (ingenol-3-angelate) and phenolics (chlorogenic acid and 4-methoxycinnamic acid), as well as coumarines (7-hydroxycoumarine, 4-methylumbelliferone, and 4-methylumbelliferyl glucuronide). Alara et al. used Soxhlet method and MAE to identify bioactive components from ethanolic extracts of *V. amygdalina*. The gas chromatography-mass spectroscopy (GC-MS) analysis was used for further identification and confirmatory test was performed utilizing fourier transform infrared spectroscopy analysis. Among the isolated and described bioactives are 2-pentanol, pentanoic acid, 2-methyl-3-hexanol, and ethyl ester linoleic acid.

3.3. *Pharmacological activities of* Vernonia amygdalina *L*

3.3.1. *Antidiarrhoeal activity*

Degu et al. (2020) investigated the antidiarrhoeal effects of *V. amygdalina* extracts against castor oil-induced diarrhoea in mice. Cold maceration with 80% methanol was used to separate *V. amygdalina* extracts. Only at the highest tested dose (400 mg/kg.bw) *V. amygdalina* showed a reduction in the beginning of diarrhoea, as well as a reduction in the frequency of stool and the weight of faeces. *V. amygdalina*'s inhibitory effects in this study highlight its antidiarrhoeal potential (Table 2). Shittu et al. (2016) evaluated the antidiarrheal activities of extracts of *V. amygdalina* against *Vibrio cholerae* induced diarrhoea mice. Single dose of 100 μL of *V. cholera* was inoculated into experimental rats. Administration of 250 mg/kg *V. amygdalina* demonstrated anti-inflammatory and anti-secretory activity in tissues of experimental mice. The inhibitory effects of *V. amygdalina* indicated in this study emphasize its antidiarrhoeal activity.

3.3.2. *Antioxidant activity*

The antioxidant activities of *V. amygdalina* have been reported by many researchers (IfedibaluChukwu et al., 2020). Iwalokun et al. (2006) investigated the anti-oxidative efficacy of *V. amygdalina* extracts against acetaminophen-induced *in vivo* toxicity in mice. Acetaminophen was injected at 300 mg/kg for 7 days. The pre-administration of the *V. amygdalina* extract at 50–100 mg/kg reduced oxidative stress. IfedibaluChukwu et al. (2020) used 2,2-diphenyl-1-picrylhydrazyl, nitric oxide, and hydrogen peroxide radical scavenging procedures in mice to investigate the anti-oxidative activities of isolates compounds from methanolic stem-bark extracts of *V. amygdalina*, they exhibited mild anti-oxidative action. Incubating brain tissues with *V. amygdalina* indicated a decrease 2-keto-glutaramic acid and cysteinyl-tyrosine metabolites in oxidative stress (Erukainure et al., 2018). Adesanoye et al. (2015) examined the chemoprotective properties of methanolic extracts of *V. amygdalina* (250 mg/kg and 500 mg/kg) against 2-acetylaminofluorene-induced hepatotoxicity in rats. by up-regulating the antioxidant enzymes. In another study, Ugbaja et al. (2021) reported the anti-oxidative activity of flavonoid fractions of *V. amygdalina* in rats exposed to arsenic-induced oxidative stress. Erasto et al. (2006) investigated the antioxidative activity of acetone, methanol and water extracts of *V. amygdalina*. The antioxidative activity of the extract was determined by detecting the reduction of the absorbance of DPPH and ABTS radicals at 519 and 734 nm, respectively. Results showed methanol extracts with highest antioxidative activity compared to the acetone and water extract. Methanolic extracts have antioxidative activity by scavenging 75.9%, 93.9%, 97.1%, and 99.3% of the DPPH radicals from 0.01, 0.02, 0.05, and 0.1 mg/ml of extracts. Acetone extracts scavenged radicals between 63.3% and 91.7%. Results from this study elucidated the antioxidative activity of *V. amygdalina.* Lolodi and Eriyamremu (2013) also examined the antioxidative activity of methanolic extract of *V. amygdalina*. The antioxidative activity of the extract was determined by treating rats with 200 mg/kg dose of *V. amygdalina* after induction with normal diet containing 5% *Cycas revoluta* (cycads). Results revealed that administration of extract induced an increase in MDA levels and reduction in SOD levels compared to the control group. Omojokun et al. (2019) revealed that extract of the plant (0–30.51 g/mL) inhibited arginase while the alkaloid from the extract reduced Fe^{2+}-induced lipid peroxidation (Table 2).

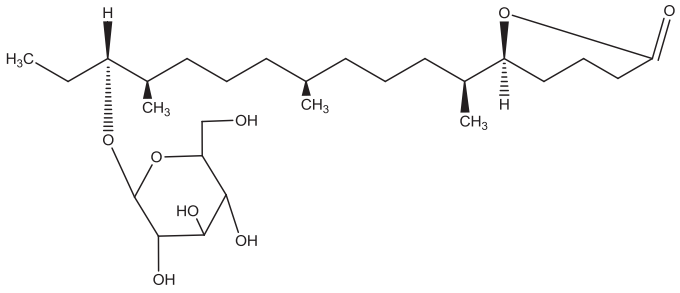
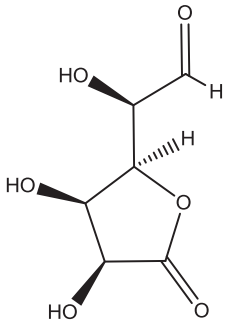
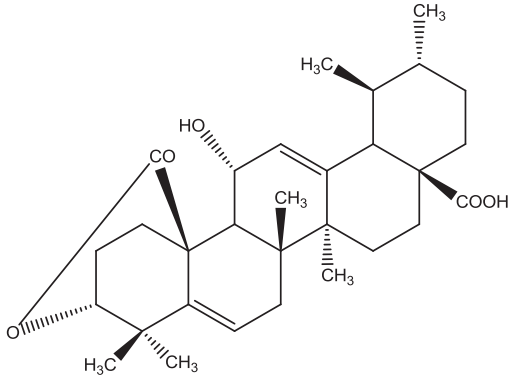
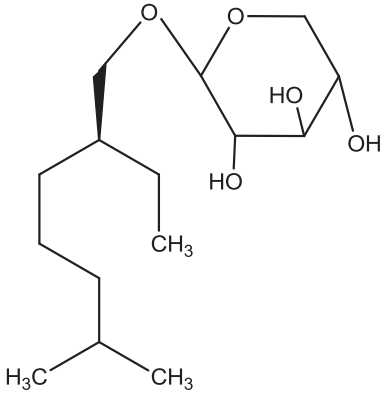
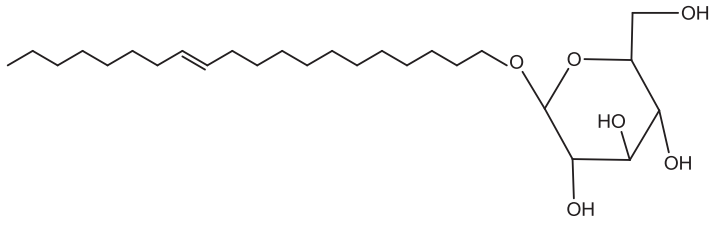
3.3.3. *Antimicrobial activity*

Studies have reported the antimicrobial activities of *V. amygdalina* (Ngatu et al., 2012; Dumas et al., 2020) showed that extracts of *V. amygdalina* exhibited inhibitory activity on all tested bacteria including *Staphylococcus aureus, Salmonella enterica* and *Klebsiella pneumoniae*. Dégbé et al. (2018) reported its inhibitory effect on *Toxoplasma gondii*, a protozoan parasite responsible for toxoplasmosis. Chloroform extract of *V. amygdalina* showed strong activity against *S. aureus* with an inhibition zone of 21 mm. Isorhamnetin and acetone extracts were active against all bacterial pathogens tested (Habtamu and Melaku, 2018). Yusoff et al. (2020) evaluated the antifungal activity of the leaf extracts against *Botrytis cinereal*. Water extract of the plant at concentration range of 100–500 mg/mL, crude extracts of hexane, dichloromethane and methanol inhibited the fungus *B. cinereal.* However, the extract of *V. amygdalina* showed the most efficacies against the fungus. Extracts from dichloromethane at 400 and 500 mg/mL showed mid severity of infection. Chukwuemeka et al. (2018) showed that the extract inhibited *S. aureus, Bacillus subtilis, Salmonella typhi and Pseudomonas aeruginosa* activities in mice. Ademola and Eloff (2011) and Abay et al. (2015) examined the acetone extracts of *V. amygdalina* to determine its antiparasitic effects against the eggs and larvae of *Haemonchus contortus*. The extract inhibited hatching of eggs and larval development, also killing off *H. contortus.* Omoregie and Pal (2016) evaluated the antiplasmodial property of *V. amygdalina* against *Plasmodium berghei* induced in male Swiss rats. *In vivo* findings showed that the ethanolic extract of the plant suppressed the activity of *P. berghei.* Oral administration of 100 and 1000 mg/kg of the plant resulted in 23.7% and 82.3% inhibition of *P. berghei* respectively at day 4 (Table 2).

3.3.4. *Immunological effect*

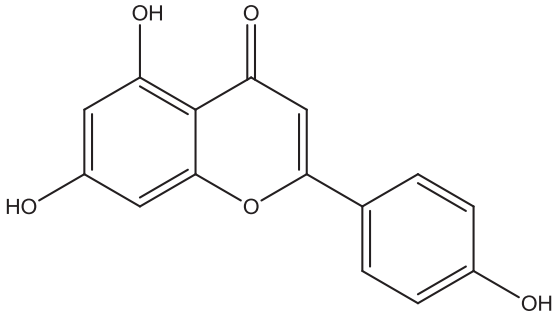
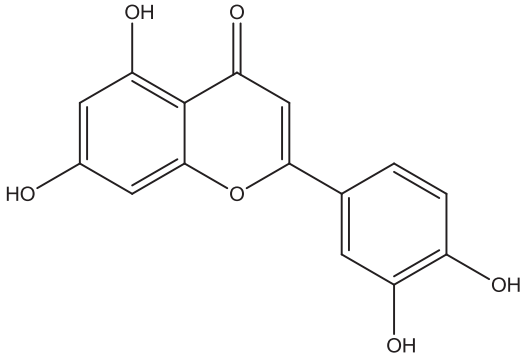
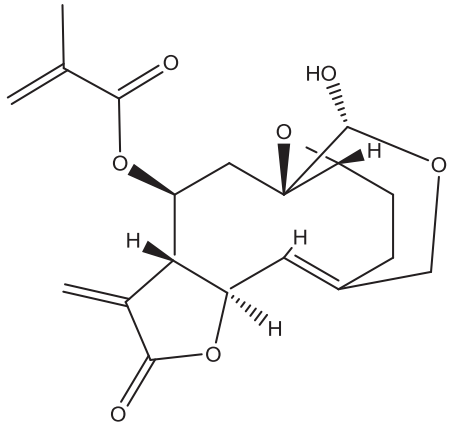
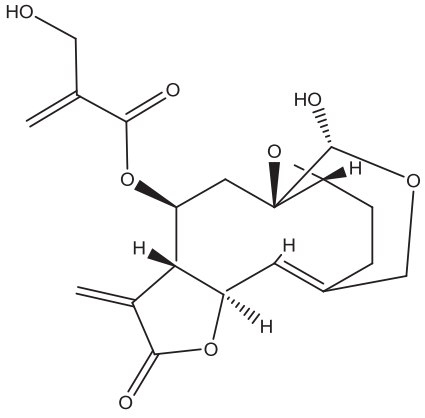
Momoh et al. (2012) studied the effect of *V. amygdalina* on $CD4^+$ cell count of HIV-infected patients on ART-regime for a year. Different doses of *V. amygdalina* and an immune booster, immunace, were administered in human clients. Results revealed an increase in $CD4^+$ cell count of infected patients. Im et al. (2016) assessed the immune-modulatory activity of *V. amygdalina* by determining its effect on the haematological and lipid parameters of *Rattus norvegicus*. Different doses including 50, 100, 200, 400 and 800 mg/kg of *V. amygdalina* were administered twice daily for 3 weeks. Results from this analysis revealed a concentration dependent increase in $CD4^+$ cell count, however, a reduction was observed at highest dose (800 mg/kg). The extract also induced an increase in white blood cells and lymphocytes.

Table 1
Biological activities of compounds isolated from *V. amygdalina*.

Bioactive Compound	Chemical Structure	Biological Activity	Reference
6 β,10 β,14 β Trimethylheptadecan-15 α-olyl-15- O-β-D-glucopyranosyl-1,5 β olide		Anti-diabetic activity, Antioxidative activity	IfedibaluChukwu et al. (2020)
Glucuronolactone		Anthelmintic activity	IfedibaluChukwu et al. (2020)
11 α-Hydroxyurs-5,12-dien-28-oic acid-3 α,25-olide		Antioxidative activity	IfedibaluChukwu et al. (2020)
10-Geranilanyl-O-β-D-xyloside		Antioxidative activity	IfedibaluChukwu et al. (2020)
1-Heneicosenol O-β-D-glucopyranoside		Antioxidative activity	IfedibaluChukwu et al. (2020)

(*continued on next page*)

Table 1 (*continued*)

Bioactive Compound	Chemical Structure	Biological Activity	Reference
Apigenin		Anticancer activity	Hasibuan et al. (2020)
luteolin(3´,4´, 5,7tetrahydroxyflavone)		Anticancer activity	Hasibuan et al. (2020)
Vernolide		Antimalarial activity	Chukwujekwu et al. (2009)
Hydroxyvernolide		Antiplasmodial, Antitumor, Antischistosoma activity	Ohigashi et al. (1994). Koshimizu et al. (1994)

(*continued on next page*)

Table 1 (*continued*)

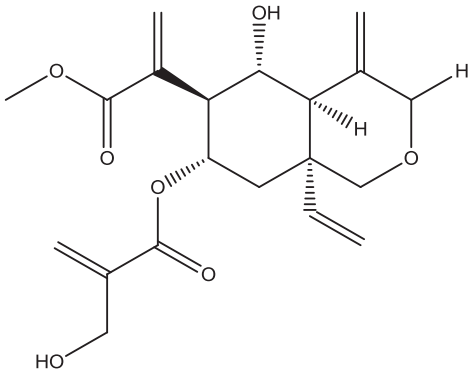
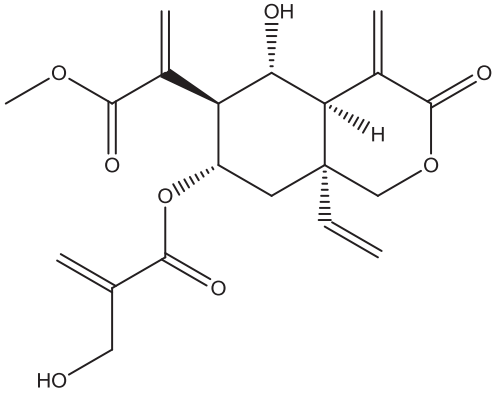
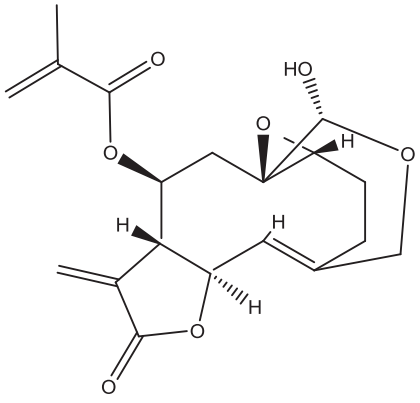
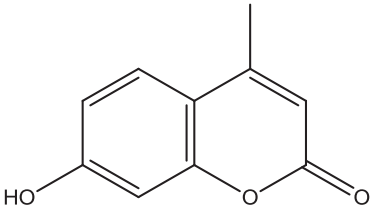
Bioactive Compound	Chemical Structure	Biological Activity	Reference
3′-deoxyvernodalol		Anti-inflammatory and Antioxidant activity	Sinisi et al. (2015)
Vernodalol		Antimicrobial, antitumoral, Antioxidant, Anti-plasmodial, Anti-schistosomal	Ohigashi et al. (1994); Erasto et al. (2006)
Vernomygdin		Anticancer activity	Oyeyemi et al. (2018)
4-methylumbelliferone		Anticancer activity	Nagy et al. (2015)

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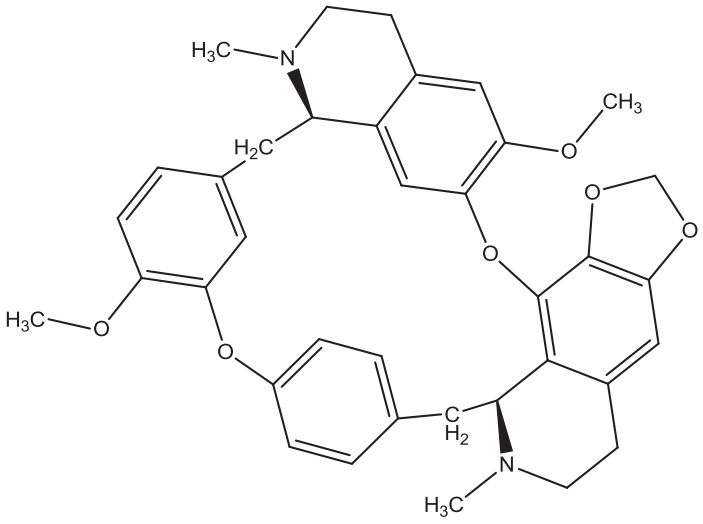
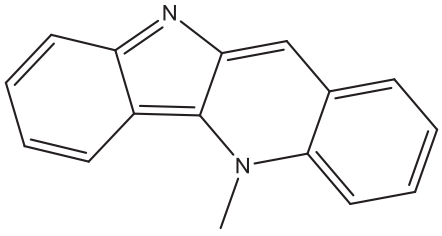
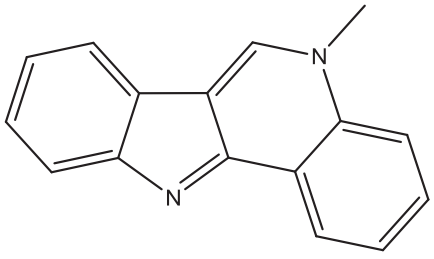
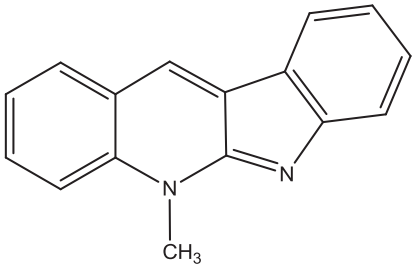
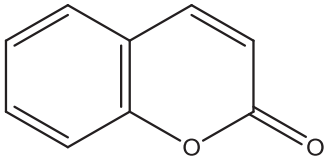
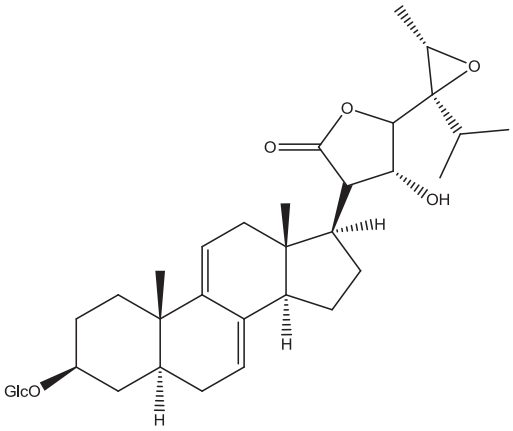
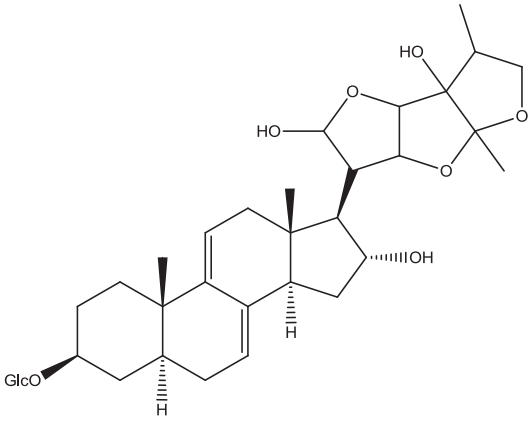
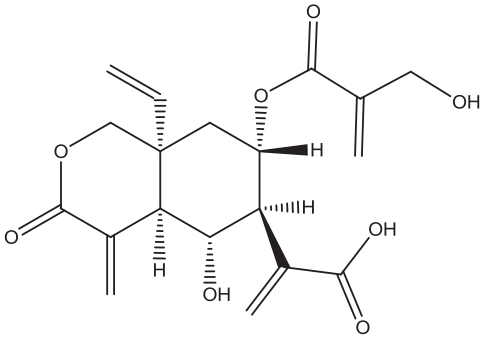
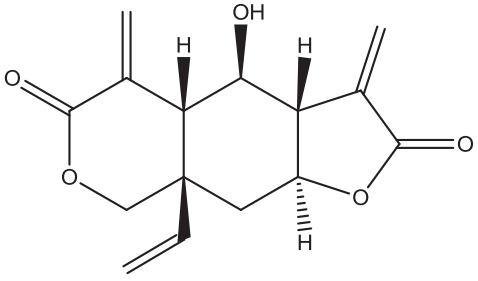
Table 1 (*continued*)

Bioactive Compound	Chemical Structure	Biological Activity	Reference
Cephantharin		Antimalarial activity	Iwalokun (2008)
Cryptolepine		Antimalarial activity	Iwalokun (2008)
Isocryptolepine		Antimalarial activity	Iwalokun (2008)
Neocryptolepine		Antimalarial activity	Iwalokun, 2008
Courmarins		Antimalarial activity	Iwalokun, 2008

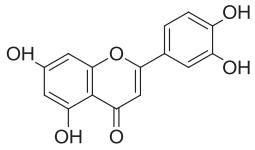
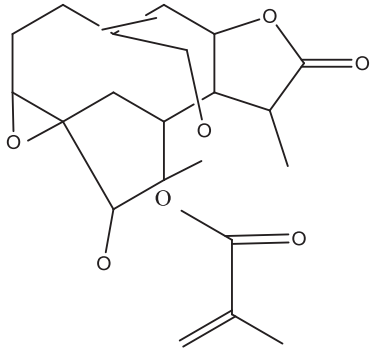
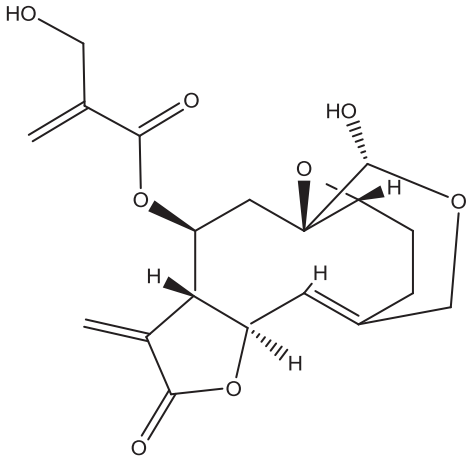
(*continued on next page*)

Table 1 (*continued*)

Bioactive Compound	Chemical Structure	Biological Activity	Reference
Vernoniosides	 **B1**  **D**	Anti-inflammatory activity Anticancer activity	Alara et al. (2017)
Vernodalinol		Antitumoral activity	Luo et al. (2011)
Vernomenin		Antiparasitic activity	Jisaka et al. (2015)

(*continued on next page*)

Table 1 (*continued*)

Bioactive Compound	Chemical Structure	Biological Activity	Reference
Luteolin			Song and Park (2014)
11 beta,13-dihydrovernolide		Antioxidative activity	Okoduwa et al. (2020)
Hydroxyvernolide		Antidiabetic activity	Koshimizu et al. (1994)

3.3.5. Anti-inflammatory activity

Studies have shown the anti-inflammatory activities of *V. amygdalina* (Nguyen et al., 2020; Liu et al., 2020) investigated the anti-inflammatory effects of cynaroside and novel vernonioside V, isolated from ethanolic extracts of leaves of *V. amygdalina.* The findings from their research showed that vernonioside V at concentration of 30 mg/mL strongly inhibited the activities of tumour necrosis α (TNFα), interleukin-6 (IL-6), and interleukin-8 (IL-8) inflammatory cytokine production. These results indicated the anti-inflammatory potentials of *V. amygdalina* isolates. Liu et al. (2020) examined synthesized zinc oxide nanoparticles from *V. amygdalina* for anti-inflammatory activity in mice (Liu et al., 2020). *V. amygdalina* reduced the inflammatory response and pro-inflammatory cytokines levels in the mice. Asante et al. (2019) assessed extracts of young and old leaves of the extract to ascertain their ability to suppress inflammation, pain, and fever in carrageenan-induced inflammation model in rats. Ethanol extracts of *V. amygdalina* were administered at 50–200 mg/kg, alongside diclofenac (10 mg/kg). The findings from the study showed a dose-dependent increase in anti-inflammatory properties observed in both ethanol extracts of young and old leaves extract, similar to the standard drugs, diclofenac. Onasanwo et al. (2017) reported that *V. amygdalina* possess anti-inflammatory effects through its ability in reducing inflammatory leukocytes migration (Table 2). These reports justify the use of *V. amygdalina* extracts in the treatment of inflammation.

3.3.6. Anticancer activity

Hasibuan et al. (2020) studied the anticancer effects of *V. amygdalina* leaves extracts on 4T1 breast cancer cells. *V. amygdalina* leaves induced apoptosis, increased cell accumulation in the G2/M phase of the cell cycle and inhibited intracellular signals such as PI3K and mTOR expression in 4T1 breast cancer cells. Yedjou et al. (2018) investigated *V. amygdalina* extract's antiproliferative efficacy against human lung cancer (A-549) and human prostate cancer (PC-3) cells. From their findings, the extract suppresses the proliferation of both A-549 and PC-3 cells in a dose-dependent manner. Yedjou et al. (2018) assessed the anticancer effects of the plant in MCF-7 cells. In the study, trypan blue exclusion test was utilized to distinguish between live and dead cells, and the propidium iodine (PI) assay with the cellometer vision was used for further analysis. Cell apoptosis was studied using flow cytometry. This study's findings revealed a reduction in cell viability in a concentration- and time-dependent manner. During the PI test, there was a steady rise in the number of necrotic cells (Table 2).

Gresham et al. (2008) investigated *V. amygdalina*'s anti-cancer efficacy in estrogen receptor-negative (ER^-) breast carcinomas. Different doses of *V. amygdalina* (10, 100, and 1000 g/mL) were given to BT-549 cells, resulting in cell growth inhibition of around 14%, 22%, and 50%, respectively. Howard et al. (2016) investigated *V. amygdalina*'s chemotherapeutic efficacy in TNBC cells and stem cell-derived tumors. The results of this experiment revealed a substantial reduc-

Table 2
Summary of the effects of *V. amygdalina* on different experimental models.

Doses	Experimental models	Observation	Effects	References
125, 250 and 500 mg/kg of *V. amygdalina*	Inoculum of 1×10^7 of *Plasmodium berghei* in mice	The extract produced 53.5% and 67% suppression of parasitaemia in 4-days.	Antimalarial activity	Abosi and Raseroka (2003)
200, 400 and 600 mg/kg of *V. amygdalina*	Inoculum of 0.2 mL *P. berghei* infected blood in mice	Produced 32.47, 35.40 and 37.67% suppression of parasitaemia in 4-days.	Antimalarial activity	Bihonegn et al. (2019)
100, 300 and 1000 mg/kg of *V. amygdalina*	Inoculum of 1×10^6 of *P. berghei* infected blood in mice	The extract produced 23.7% and 82.3% suppression of parasitaemia in 4-days.	Antimalarial activity	Omoregie and Pal (2016)
350 mg/kg of *V. amygdalina*	Inoculum of 2.5×10^7 *P. berghei* in mice	The extract resulted in the reduction of parasite load in mice	Antimalarial activity	Okpe et al. (2016)
31.25, 62.5 and 125 mg/kg of *V. amygdalina*	Inoculum of 10^6 of *P. berghei* in mice	The extract induced 57.2- 72.7% suppression of parasitaemia in 4-days.	Antimalarial activity	Iwalokun (2008)
10, 50, 100 and 200 mg/kg of *V. amygdalina*	0.5% of *Plasmodium falciparum* and 1% haematocrit.	The extract produced antimalarial activity of5.9%, 17.5%, 49.4%, and 88.5%, respectively.	Antimalarial activity	Masaba (2000)
400, 600, and 800 mg/kg of *V. amygdalina*	1×10^6 *P. berghei* parasitemia in mice	The extracts had a suppressive effect of 17.94% in parasitemia against 46.53% of negative control.	Antimalarial activity	Yeshanew et al. (2021)
200 and 400 mg/kg of *V. amygdalina*	100 mg/kg of nitrobenzene in rats for 14 days	Increased the levels of antioxidant enzymes, dopamine and reduced the activity of acetylcholinesterase.	Neuroprotective activity	Oladele et al. (2020)
200, 100 and 50 mg/kg doses of *V. amygdalina*	300 mg/kg of acetaminophen for 7 days in mice	Acetaminophen- induced alterations occurring on the liver function parameters were reduced.	Hepatoprotective activity	Iwalokun et al. (2006)
250 and 500 mg/kg doses of *V. amygdalina*	100 mg/kg of 2-acetylaminofluorene for 7 days in mice	Increased glutathione and antioxidant defence enzymes.	Hepatoprotective activity	Adesanoye et al. (2013)
250, 500 and 750 mg/kg doses of *V. amygdalina*	1.2 g/kg of carbon tetrachloride administered 3 times in a week for 3 weeks in rats	Decreased cholesterol, triglyceride, and phospholipid concentrations and increased antioxidant enzymes.	Hepatoprotective activity	Adesanoye and Farombi (2010)
50 and 100 mg/kg of *V. amygdalina*	27 and 54 mg/kg of isoniazid (INH) and rifampicin respectively in rats for 35 days	Inhibited liver intoxication.	Hepatoprotective activity	Iwo et al. (2017)
100, 200 and 400 mg/kg of *V. amygdalina*	5 mg/kg of cadmium for 5 days in rats	Attenuated Cd-induced alterations in liver biomarkers (AST, ALT, ALP, total bilirubin) and decreased oxidative stress indicators.	Hepatoprotective activity	Imafidon et al. (2018)
200, 400 and 800 mg/kg of *V. amygdalina*	400 rads from ^{60}Co gamma chamber in a single dose.	Induced a reduction in levels of serum liver enzymes and caused 29% reduction of serum bilirubin.	Hepatoprotective activity	Adaramoye et al. (2008a)
100, 200 and 300 mg/kg of *Vernonia amygdalina*	13 mg/kg Pb and 16 mg/kg Cu in separate treatment groups for 14 days.	Extract ameliorated heavy metal induced toxicity by reduction of elevated ALT, AST, GGT, urea and creatinine levels.	Hepatoprotective activity	Barnes et al. (2020)
Different doses of *V. amygdalina* combined with immunace	40 HIV-infected patients on ART regimen.	Increased CD4 count by 4%. Combined dose of *V. amygdalina* and immunace increased CD4 count by 12%.	Immunological activity	Momoh et al. (2012)
50, 100, 200, 400 and 800 mg/kg of *V. amygdalina*	Healthy *Rattus norvegicus* fed extracts twice daily for 3 weeks.	Induced an increase in $CD4^+$ cell counts, white blood cells and lymphocytes.	Immunological activity	Im et al. (2016)
10, 30 and 300 mg/kg doses of *V. amygdalina*	40 mg/kg of STZ for 3 days in mice.	Antihyperglycemic activity.	Anti-diabetic activity	Asante et al. (2016)
500 mg/kg of *V. amygdalina*	40 mg/kg of STZ (single dose) in rats.	Reduced blood glucose levels.	Anti-diabetic activity	Tekou et al. (2018)
200, 400 and 500mg/kg of *V. amygdalina*	Single dose of 55 mg/kg of STZ in rats.	Reduced hepatic glucogenic enzymes: glucose 6-phosphatase, fructose 1,6-bisphosphatase and phosphoenol pyruvate carboxykinase.	Anti-diabetic activity	Atangwho et al., 2012
200, 400, 600 mg/kg of *V. amygdalina*	Single dose of 55 mg/kg of STZ in rats	Reduced fasting blood glucose.	Anti-diabetic activity	Ong et al. (2011)
200 mg/kg combined dose of *V. amygdalina* and *Azadirachta indica*	Single dose of 65 mg/kg of STZ in rats	Reduced blood glucose.	Anti-diabetic activity	Atangwho et al. (2012).
100 mg/kg of *V. amygdalina* in combined ratio with metformin	Single dose of 150 mg/kg of alloxan monohydrate in rats	The extracts in ratios of 1:2 and 2:1 decreased blood sugar levels.	Anti-diabetic activity	Michael et al. (2010)
150 ml of *Vernonia amygdalina, Gongronema latifolium and Occimum gratissimum*	75 g of white bread in humans observed during a period of 120 min	The decoction induced a reduction in blood glucose levels.	Anti-diabetic activity	Ejike et al. (2013)
50, 100, 150 mg/kg of *V. amygdalina* extracts.	Single dose of 60 mg/kg of STZ in mice after 12 hours of fasting.	Reduced fasting blood glucose.	Anti-diabetic activity	Wu et al. (2018)
52 mg/kg of *V. amygdalina* and 208 mg/kg of *O. gratissimum*	Single dose of 65 mg/kg of STZ	Reduced the blood glucose concentration.	Anti-diabetic activity	Okon and Umoren (2017)

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Table 2 (*continued*)

Doses	Experimental models	Observation	Effects	References
100 and 400 mg/kg of *V. amygdalina*	Single dose of 150 mg/kg of alloxan in rats	Reduced glucose levels.	Anti-diabetic activity	Owolabi et al. (2011)
400 mg/kg of *V. amygdalina*	Single dose of 65 mg/kg of STZ in rats	Reduced fasting blood glucose.	Anti-diabetic activity	Ong et al. (2011)
100 and 200 mg/kg doses of *V. amygdalina*	30 mg/0.3ml of cholesterol five times weekly for 9 consecutive weeks in rats	Reduced post mitochondrial fraction and plasma cholesterol.	Lipid-lowering activity	Adaramoye et al. (2008a)
2.5, 5.0, 7.5 mg/kg doses of zinc oxide nanoparticles of *V. amygdalina*	Intraperitoneal administration of 1% acetic acid in mice observed for 30 mins	Reduced in the number of writhes.	Anti-inflammatory activity	Liu et al. (2020)
Doses of *V. amygdalina* ranging from (50–200 mg/kg)	100 μL of 2% carrageenan in rats.	2 hours post treatment results showed reduction in oedema.	Anti-inflammation activity	Asante et al. (2019)
200 mg/kg doses of *V. amygdalina*	2 ml of 2% carrageenan dissolved in saline solution inoculated in pouch cavity of rats	The extract in combined dose with indomethacin (5 mg/kg) produced a decrease in total leukocytes.	Anti-inflammatory activity	Onasanwo et al. (2017)
0 μg/mL, 125 μg/mL, 250 μg/mL, and 500 μg/mL doses of *V. amygdalina*	1×10^6 cells/mL of HL-60 promyelocytic leukemia cells after incubated for 24 hours.	The extracts induced DNA damage and cell apoptosis.	Acute promyelocytic and leukemia treatment	Yedjou et al. (2018)
125, 250, and 500 μg /mL doses of *V. amygdalina*	Human prostate cancer (PC-3) cells treated with *V. amygdalina* extracts for 48 hours	Antiproliferative activity with an IC_{50} value of 196.6 μg /mL. Inhibited cell growth, damaged DNA, and induced cell apoptosis.	Anticancer activity	Johnson et al. (2017)
0-1000 µg/ml of *V. amygdalina*	5×10^5 and 4×10^4 of MCF-7 cells	Inhibited cell growth under serum-free conditions	Anticancer activity	Opata and Izevbigie (2006)
125, 250, and 500 μg/mL doses of *V. amygdalina*	(A-549) human lung cancer cells and (PC-3) human prostate cancer cells treated for 48 hours.	The extracts (in a dosage-dependent manner) suppressed the proliferation activity of the (A-549 and PC-3) cells.	Anticancer activity	Yedjou et al. (2018)
250, 500, and 1000 μg/mL of *V. amygdalina*	1×10^6 cells/mL of human breast adenocarcinoma (MCF-7) cells	Induced early signs of apoptosis after 48 hours of examination due to phosphatidylserine externalization.	Anticancer activity	Yedjou et al. (2013)
10, 100, 1000 μg/mL of *V. amygdalina*	Human ductal carcinoma cell line (BT-549) observed for 24 hours	14 %, 22 %, and 50 % growth inhibition was induced by 10, 100, 1000 μg/mL of extracts respectively.	Anticancer activity	Gresham et al. (2008)
Doses of *V. amygdalina* ranging from 0-200 μg/kg	5×10^3 of MCF-7 and MDA-MB-231 cells	Inhibited cell growth by stimulation of G1/S phase cell cycle arrest, induced an increase in p53 and p21 levels.	Anticancer activity	Wong et al. (2013)
0.01, 0.1 and 1 mg/ml of *V. amygdalina*	Androgen independent prostate adenocarcinoma (PC-3 cells)	Induced an inhibition of DNA synthesis and NF-B activation, and stimulated activation of MAPK.	Anticancer activity	Cameron et al. (2013)
150 μl/ml of 15–240 μg/ml of *V. amygdalina*	75 μl of 0.3 mM of 1,1-diphenyl-2picrylhdrazyl in rats	α-glucosidase and pancreatic lipase activity was inhibited by the extracts.	Antioxidative activity	Erukainure et al. (2018)
100, 200, and 400 mg/kg dose of *V. amygdalina*	0.5 ml of castor oil in mice	Reduced the frequency of wet defaecation.	Antidiarrheal activity	Degu et al. (2020)
100, 200, and 400 mg/kg dose of *V. amygdalina*	0.5 ml of castor oil in mice	Reduced the frequency of wet and total stool as well as prolonged the onset of diarrhoea.	Antidiarrheal activity	Gudeta et al. (2020)
200, 300, and 400 mg/kg of *V. amygdalina*	150 mg/kg of aspirin for 3 days in mice	Reduced pepsin activity, gastric volume, malondialdehyde level and free and total acidity.	Gastroprotective activity	Adefisayo et al. (2018)
200, 300 and 400 mg/kg of *V. amygdalina*	150 mg/kg of aspirin for 3 days in mice	Lowered gastric ulcer score, gastric acid secretion, white blood cell count and granulocytes.	Gastroprotective activity	Adefisayo et al. (2017)
Extracts of *V. amygdalina* supplemented with Cafeteria diet at 5% at 15%.	5.14 mg/kg of Orlistat for 4 weeks in rats	Reduced body weight and total body fat.	Anti-obesity activity	Atangwho et al. (2012)
5% and 15% of *V. amygdalina* supplemented with cafeteria-diet	Cafeteria diet inducing fat in Wistar rats and 5.14 mg/kg of Orlistat in treatment groups.	Reduced body weight and total body fat.	Anti-obesity activity	Atangwho et al. (2012)
Different doses of *V. amygdalina* at (25–150 $mgml^{-1}$)	Erythrocytes from human blood incubated with tert-butyl hydroperoxide for 6 hours.	Suppression of t-BHP induced electrolysis.	Prevention of haemolysis	Adesanoye et al. (2013)
20 μl of *V. amygdalina*	150 μL of 5 % of 2,4,6-trinitrochlorobenzene, subsequently 15 μL of 1 % trinitrochlorobenzene administered once in 3 days in mice.	Inhibited the development of atopic dermatitis and reduced the number of scratching behaviours in mice.	Anti-allergic effect	Ngatu et al. (2012)
25 mg/ml of *V. amygdalina*	*Bacillus subtilis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Shigella dysenteriae* and *Proteus ulgaris*	These bacteria were sensitive to *V. amygdalina* at 25 mg/ml, while *E. coli* and *S. marcescens* showed resistance.	Antimicrobial activity	Akinpelu (1999)

tion in tumor volume in MDA-MB-468 cells when compared to HRAS cells. *V. amygdalina* increased cell apoptosis which inhibits tumour development, justifying its chemoprotective effect (Howard et al., 2016). Wong et al. (2013) revealed that the extract of *V. amygdalina* was shown to inhibit the proliferation of MCF-7 and MDA-MB-231 in a time- and dose-dependent manner through 3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide (MTT) assay. Growth suppression in MCF-7 cells was supplemented by inducing cell-type specific G1/S phase cell cycle arrest. In the study, the ability of *V. amygdalina* to suppress growth was characterized by a decrease in certain signalling factors including cyclin D1 and cyclin E levels, and an increased in p53 and p21 levels. The extract induced cell apoptosis, as evidenced by an increase in Annexin V-positive cells and the sub-G1 population.

Other studies that reported the anticancer activities include Hasibuan et al. (2020) investigated the anticancer efficacy of the extracts against 4T1 breast cancer cells. Bestari et al. (2018) examined its anti-cancer activity against WiDr colon cancer cell line. The researchers showed that the ethyl acetate extract of *V. amygdalina* possesses strong cytotoxic potential having the lowest IC_{50} value (Bestari et al., 2017). Cameron et al., 2013 examined the anticancer activity of extracts of *V. amygdalina* against androgen independent prostate adenocarcinoma (PC-3 cells). [^{3}H] thymidine incorporation assays were used to determine DNA synthesis. Values obtained from the results showed an inhibition of DNA synthesis 12%, 45% ($P < 0.05$), and 73% ($P < 0.01$) upon administration of extract at 0.01, 0.1 and 1 mg/ml doses. Extract resulted in a time-dependent activation of MAPK activity. Result showed more anti-cancer activity compared to Taxol protective activity. These results showed the anticancer activity of *V. amygdalina*. Opata and Izevbigie (2006) examined the anticancer activity of *V. amygdalina* in MCF-7 cells. 0–1000 μg/ml of *V. amygdalina* was inoculated into the cells. Extract at (0, 30, and 100 μg/ml) of *V. amygdalina* inhibited [^{3}H] thymidine uptake. Extract (1 and 10 μg/ml) inhibited cell growth by 40% and 54% under serum-free conditions. Chukwuemeka et al. (2018) investigated the anticancer efficacy of the plant's stem and leaves in mice, while Yedjou et al. (2018) investigated the extracts for anti-cancer efficacy against human breast cancer *in vitro* (Table 2). Wang et al. investigated the cytotoxic activity of isolated steroidal saponins from *V. amygdalina*, namely vernoniamyosides A–D (1–4), vernoamyoside D (5), and vernonioside B2 (6). Vernoniamyoside A, vernoniamyoside B, and vernoniamyoside B2 were shown to be cytotoxic to BT-549 cell lines. Vernoniamyoside C, vernoniamyoside D, and vernoamyoside D exhibited varying degrees of cytotoxicity. The findings of this study provide a substantial basis for the use of *V. amygdalina* in anti-tumour research while also explaining its anti-cancer potential (Wang et al., 2018) (Table 2). Fachrunisa et al. (2019) investigated the cytotoxic activity, cell cycle inhibition, and apoptosis induction characteristics of *V. amygdalina* leaves' ethyl acetate extract on MCF-7 cancer cells. Treatment with ethyl acetate extract 1/2 IC_{50} and 1/5 IC_{50} resulted in cell cycle at 62.58% and 44.72%, respectively, compared to the cell control of 72.08%. These findings support *V. amygdalina* leaves' chemopreventive and anticancer properties.

3.3.7. Anti-diabetic activity

Studies have reported the anti-diabetic activities of *V. amygdalina* (IfedibaluChukwu et al., 2020). Asante et al. (2019) evaluated the anti-diabetic effects of young and old ethanolic leaf extracts of the resource plant against streptozotocin (STZ) induced diabetes in mice. IfedibaluChukwu et al. (2020) showed that isolated compounds from methanolic stem-bark extracts of *V. amygdalina* like 6β,10β,14β-trimethylheptadecan-15 α-olyl-15-O-β-D-glucopyranosyl-1,5 β-olide had a significant reduction in the blood glucose in STZ-induced diabetic rats. Another study reported by Tekou et al. (2018) showed that oral administration of *V. amygdalina* for 4 weeks ameliorated type 2 diabetes in rats that were induced with STZ. Erukainure et al. (2019) revealed that hot water infusion of the leaves of *V. amygdalina* had inhibitory activity against α-glucosidase, reduced intestinal glucose absorption, and enhanced muscle glucose uptake. Ong et al. (2010) showed that the protective actions of the extract on β-cells resulted in a rise in insulin levels and the favourable regulation of the antioxidant system may be responsible to its anti-diabetic activity. *V. amygdalina* increased skeletal muscle glucose uptake by boosting GLUT 4 translocation to the plasma membrane (Table 2).

Michael et al. (2010) reported that the combination of *V. amygdalina* extract with metformin was potent against alloxan-induced diabetes in mice. Okon and Umoren (2017) investigated the antidiabetic activity of *V. amygdalina* against STZ (65 mg/kg) in type 1 diabetic rats. 52 mg/kg of *V. amygdalina* and 208 mg/kg of *Ocimum gratissimum* were administered orally for 28 days. Results revealed a hypoglycemic activity of *V. amygdalina* extracts. Owolabi et al. (2011) assessed the blood glucose lowering activity of *V. amygdalina* extracts against alloxan-induced diabetes in mice. Wu et al., 2018 assessed the antidiabetic effects of *V. amygdalina* against STZ-induced diabetes in mice. After 6 weeks of treatment with 50, 100, 150 mg/kg of *V. amygdalina* extracts revealed a reduction in fasting blood glucose and also improved glucose and insulin resistance. Extract also induced an up-regulation in adenosine-5'monophosphate kinase enzymes and inhibition of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase. From the results obtained it can be concluded that extracts of *V. amygdalina* has antidiabetic activity.

3.3.8. Hepatoprotective activity

Iwalokun et al. (2006) investigated the *in vivo* hepatoprotective properties of *V. amygdalina* extracts against acetaminophen-induced liver damage in mice. Pretreatment with the extract at doses ranging from 50 to 100 mg/kg alleviated the induced acetaminophen changes in liver function parameters by 51.9% to 84.9%. Adesanoye and Farombi (2010) studied the effects of methanolic extracts of *V. amygdalina* against carbon tetrachloride (CCl_4) in male rats. Hepatic injury was induced by administering CCl_4 orally at 1.2 g/kg 3 times a week for 3 weeks. Methanolic extracts of the plant were administered 5 times a week for 2 weeks prior CCl_4 treatment at 250 and 500 mg/kg doses of extract. Administration of the extract elevated the activities of antioxidant enzymes at 500 mg/kg concentration. Iwo et al. (2017) reported hepatoprotective effects of *V. amygdalina* extracts on intoxicated rats in combination with isoniazid and rifampicin (Table 2). Results from assessed serum albumin concentration and alanine amino transferase activity showed that the 100 mg/kg extract had hepatoprotective effect. Furthermore, the histological reports also revealed a minimal liver damage at 100 mg/kg.

Barnes et al. (2020) examined the protective activity of *V. amygdalina* extracts against heavy metal induced toxicity in liver and kidney. After 21 days of the extract administration, there were reduction in elevated levels of AST, ALT, and GGT, urea and creatinine. Adaramoye et al. (2008b) investigated the hepatoprotective effects of *V. amygdalina* and *Hibiscus sabdariffa*, as well as vitamin C, against gamma radiation (4 Gy)-induced liver damage in rats. The mice were given a vitamin C dose of 250 mg/kg. Doses of 200, 400 and 800 mg/kg of *V. amygdalina* and *Hisbiscus sabdariffa* were given 4 weeks before and 5 weeks after radiation. The mice were sacrificed after 24 hours. At 24 hours, 800 mg/kg of *V. amygdalina* and vitamin C mixed extract resulted in an increase in blood alanine aminotransferase and aspartate aminotransferase activity. At 800 mg/kg, *V. amygdalina* extract reduced blood conjugated bilirubin levels by 29%. The treatment resulted in a decrease in serum lipid peroxidation and an increase in hepatic superoxide dismutase levels. Vitamin C and *V. amygdalina* extracts at 400 and 800 mg/kg substantially reduced alkaline phosphatase and LPO levels. These findings also suggested hepatoprotective effect of the extract via anti-oxidative activities (Table 2).

3.3.9. Neuroprotective properties

Oladele et al. (2020) investigated the neuroprotective mechanism of *V. amygdalina* methanolic leaf extract in rats with nitrobenzene-induced

neurological disease. The findings revealed a rise in dopamine, glutathione, and antioxidant enzyme levels, as well as a decrease in acetylcholinesterase activity, inflammatory and oxidative stress indicators. The findings of the study provide evidence for the therapeutic benefits of *V. amygdalina* methanol leaf extract on neurodegenerative diseases (Table 2).

3.3.10. Antimalarial activity

Abosi and Raseroka (2003) tested the extracts of *V. amygdalina*'s leaves and root bark for antimalarial efficacy against drug-resistant *P. berghei* in mice. A standard inoculum of 1×10^7 infected erythrocytes was utilized, and leaf and root-bark extracts at doses of 125, 250, or 500 mg/kg were given for 4 days. The results indicated that leaf and root bark extracts had a suppression level by 67% and 53.5%, respectively (Table 2). The study's findings demonstrate that administering an ethanol extract of *V. amygdalina* during early infection can reduce parasitaemia. Bihonegn et al. (2019) tested the antimalarial activity of an 80% methanol extract and its solvent fractions of *V. amygdalina* leaves against *P. berghei* in mice. The extract produced a suppression of parasitaemia during a 4-day test in the following order 200mg/kg; 32.47% (±2.65), 400mg/kg; 35.40% (±3.14) and 600mg/kg; 37.67% (±2.50). Okpe et al. (2016) discovered a rise in red blood cells and a recovery in packed cell volume in *V. amygdalina* treated groups in *Plasmodium* infected mice. Hepatic cells that had been injured by *Plasmodium* recovered after being given plant extracts. Challand and Willcox (2009) investigated the leaves of *V. amygdalina* for their efficacy in the treatment of unfinished malaria in patients aged 12 years and older. According to the findings of this study, 67% of patients had satisfactory clinical responses by day 14. Although 32% of these patients reported full parasite removal, 71% had recrudescence. Furthermore, no adverse effects were noted. Abay et al., 2015 investigated *V. amygdalina's* antimalarial efficacy against *P. berghei* in mice. Aqueous (Ver-H_2O) and ethanolic (Ver-EtOH) leaf extracts were tested for their effectiveness against *P. berghei* sexual and asexual blood stages. The density of *P. berghei* was reduced by 50% due to Ver-H_2O intake. *P. berghei* oocyst prevalence and density were decreased by 27% and 90%, respectively, when Ver-EtOH were administered. *In vitro* testing of 50 µg/mL Ver-EtOH revealed a high effectiveness in inhibiting early sporogenic stage (ESS) formation (> 90%). Four fractions produced at this concentration from the ethylacetate phase of the methanol extract inhibited ESS (> 90%). These findings indicate that *V. amygdalina* includes its compounds have a strong antimalarial activity in *Plasmodium* stages.

Yeshanew et al. (2021) examined the antimalarial activity of *V. amygdalina* in mice infected with 1×10^6 *P. berghei* parasitemia. Administration of extract began after 3 hours of inoculation with 400, 600, and 800 mg/kg of the extract administered orally for 4 consecutive days. Parasitemia levels observed in highest treatment group was low 17.94±0.31 compared to the negative control group 46.53±1.23. Iwalokun (2008) showed combination antimalarial effect of *V. amygdalina* extracts and chloroquine (5 mg/kg) in the range (57.2-72.7%). The extract also reduced parasitic clearance times. In contrast to chloroquine monotherapy, combination of chloroquine and *V. amygdalina* resulted in a higher cure rate in *P. berghei*-infected mice (66.7 – 100 vs. 58.3%). These findings highlight *V. amygdalina*'s antimalarial potential, demonstrating how extracts restore the effectiveness of chloroquine against *P. berghei* malaria in mice in a dose-dependent manner (Iwalokun, 2008). Masaba, 2000 investigated the antimalarial effects of *V. amygdalina* on *P. berghei* obtained from a school kid and kept in liquid nitrogen *in vitro*. These experiments revealed that acetone-water and aqueous extracts of *V. amygdalina* have antimalarial activity, with the acetone-water extract being more effective (Table 2). These findings revealed *V. amygdalina* extracts' antimalarial activity.

3.3.11. Analgesic activity

Njan et al. (2008) investigated the antinociceptive effect of *V. amygdalina* extracts (acetic acid-induced writhing, formalin test, and tail-flick test) (Table 2). The extract inhibited acetic acid-induced writhing and the formalin test, according to the results of this test.

3.3.12. Cathartic effect

Awe et al. (1999) investigated the cathartic effect of *V. amygdalina* using charcoal meal administered in mice. 50, 100 and 200 mg/kg of *V. amygdalina* were administered to mice in different groups. Results revealed increased motility of charcoal meal and increased number of feaces. These results emphasized the purgative activity of *V. amygdalina*.

3.3.13. Anti-obesity activity

Egedigwe et al. (2016) examined the anti-obesity activity of *V. amygdalina* in rats induced with high-fat diet. Rats were administered with 100 mg/kg.bw and 500 mg/kg.bw of aqueous extracts of *V. amygdalina*. Results showed a loss in weight of rats due to phytochemicals present in *V. amygdalina*, also reduction in insulin and leptin levels were observed in the extract treated groups. Atangwho et al. (2012) assessed the anti-obesity activity of *V. amygdalina* in diet induced obese rats. Extracts of *V. amygdalina* were administered at 5% and 15% supplemented with cafeteria-diet-fed to the treatment groups. Cafeteria-diet control group was administered 5.14 mg/kg of Orlistat. Results showed a reduction in body weight gain by 12.78% and 38.51% in treatment groups. Total body fat was reduced by 28.04% and 30.02% by 5% and 15% of *V. amygdalina*, respectively. Intake of 15% *V. amygdalina* induced a down regulation of serum triacylgycerol, serum and brain total cholesterol (Table 2).

3.4. Conclusion

From the review, *Vernonia amygdalina* displays outstanding pharmaceutics and nutritional uses, making it a great functional component utilized in the treatment of a variety of health abnormalities. This plant may be a superior substitute for traditional medication in the treatment of microbial infections, cancer, diarrhoea, anaemia, and inflammatory disorders since it is a good source of essential phytochemicals, nutrients, and bioactive isolates with a higher biological value. *V. amygdalina* extracts improve health by boosting antioxidant activity and systems. Despite *V. amygdalina*'s extensive pharmacological activity, additional human clinical studies are required to discover effective and safe dosages for the treatment of various diseases.

Ethical Approval

Not applicable.

Data Availability

Nil.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

EAU conceived the work, sourced literature, drafted and edited the original paper. OE sourced literature, drafted the original paper, read, and edited the manuscript. EDD wrote the initial draft and edited the manuscript. GOA, CI, OCU and EJI read and edited the original draft. All authors read and accepted the responsibility for the content of this manuscript.

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References

Abay, SM, Lucantoni, L, Dahiya, N, Dori, G, Dembo, EG, Esposito, F, Lupidi, G, Ogboi, S, Ouédraogo, RK, Sinisi, A, Taglialatela-Scafati, O, Yerbanga, RS, Bramucci, M, Quassinti, L, Ouédraogo, JB, Christophides, G, Habluetzel, A., 2015. Plasmodium transmission blocking activities of *Vernonia amygdalina* extracts and isolated compounds. Malar J 14, 288. doi:10.1186/s12936-015-0812-2.

Abosi, AO, Raseroka, BH., 2003. In vivo antimalarial activity of Vernonia amygdalina. J Biomed Sci 60, 89–91. doi:10.1080/09674845.2003.11783680.

Adaramoye, OA, Akintayo, O, Achem, J, Fafunso, MA., 2008a. Lipid-lowering effects of methanolic extract of *Vernonia amygdalina* leaves in rats fed on high cholesterol diet. Vasc Health Risk Manag 4 (1), 235–241. doi:10.2147/vhrm.2008.04.01.235.

Adaramoye, O, Ogungbenro, B, Anyaegbu, O, Fafunso, M., 2008b. Protective effects of extracts of *Vernonia amygdalina, Hibiscus sabdariffa* and vitamin C against radiation-induced liver damage in rats. J Radiat Res 49 (2), 123–131. doi:10.1269/jrr.07062.

Adefisayo, MA, Akomolafe, RO, Akinsomisoye, SO, Alabi, QK, Ogundipe, OL, Omole, JG, Olamilosoye, KP., 2017. Gastro-protective effect of methanol extract of *Vernonia amygdalina* (del.) leaf on aspirin-induced gastric ulcer in Wistar rats. Toxicol Rep 13 (4), 625–633. doi:10.1016/j.toxrep.2017.11.004.

Adefisayo, MA, Akomolafe, RO, Akinsomisoye, OS, Alabi, QK, Ogundipe, L, Omole, JG, Olamilosoye, KP., 2018. Protective effects of methanol extract of *Vernonia amygdalina* (*del.*) Leaf on Aspirin-Induced Gastric Ulceration and Oxidative Mucosal Damage in a Rat Model of Gastric Injury. Dose Response doi:10.1177/1559325818785087.

Ademola, IO, Eloff, JN., 2011. Anthelminthic activity of acetone extract and fractions of *Vernonia amygdalina* against *Haemonchus contortus* eggs and larvae. Trop Anim Health Prod 43 (2), 521–527. doi:10.1007/s11250-010-9727-7.

Adesanoye, OA, Adekunle, AE, Adewale, OB, Mbagwu, AE, Delima, AA, Adefegha, SA, Molehin, OR, Farombi, EO., 2015. Chemoprotective effect of *Vernonia amygdalina* Del. (Astereacea) against 2-acetylaminofluorene-induced hepatotoxicity in rats. Toxicol Ind Health 32 (1), 47–58. doi:10.1177/0748233713498436.

Adesanoye, OA, Farombi, EO., 2010. Hepatoprotective effects of *Vernonia amygdalina* (astereaceae) in rats treated with carbon tetrachloride. Exp Toxicol Pathol 62 (2), 197–206. doi:10.1016/j.etp.2009.05.008.

Adesanoye, OA, Molehin, OR, Delima, AA, Adefegha, AS, Farombi, EO., 2013. Modulatory effect of methanolic extract of Vernonia amygdalina (MEVA) on tert-butyl hydroperoxide-induced erythrocyte haemolysis. Cell Biochem Funct 31 (7), 545–550. doi:10.1002/cbf.2933.

Akah, PA, Ekekwe, RK., 1995. Ethnopharmacology of some of the asteraceae family used in the Nigerian traditional medicine. Fitoterapia 66, 352–355.

Akinpelu, DA., 1999. Antimicrobial activity of *Vernonia amygdalina* leaves. Fitoterapia 70 (4), 432–434. doi:10.1016/S0367-326X(99)00061-1.

Alabi, QK, Adeyemi, WJ., 2021. *Vernonia amygdalina* (Del) as an antioxidant, aspirin toxicity, and oxidative stress. Toxicology 491–504. doi:10.1016/B978-0-12-819092-0.00048-0.

Alara, OR, Abdurahman, NH, Mudalipa, SKA, Olalere, OA., 2017. Phytochemical and pharmacological properties of *Vernonia amygdalina*: a review. Journal of Chemical Engineering and Industrial Biotechnology 2, 80–96. doi:10.15282/JCEIB-V2-07.29/9/2017/2.2.

Amira, OC, Okubadejo, NU., 2007. Frequency of complementary and alternative medicine utilization in hypertensive patients attending an urban tertiary care centre in Nigeria. BMC Complement Altern Med 7, 30. doi:10.1186/1472-6882-7-30.

Asante, DB, Henneh, IT, Acheampong, DO, Kyei, F, Adokoh, CK, Ofori, EG, Domey, NK, Adakudugu, E, Tangella, LP, Ameyaw, EO., 2019. Anti-inflammatory, anti-nociceptive and antipyretic activity of young and old leaves of *Vernonia amygdalina*. Biomed Pharmacother 111, 1187–1203. doi:10.1016/j.biopha.2018.12.147.

Atangwho, IJ, Edet, EE, Uti, DE, Obi, AU, Asmawi, MZ, Ahmad, M., 2012. Biochemical and histological impact of *Vernonia amygdalina* supplemented diet in obese rats. Saudi J Biol Sci 19 (3), 385–392. doi:10.1016/j.sjbs.2012.05.003.

Atangwho, IJ, Ebong, PE, Eyong, EU, Asmawi, MZ, Ahmad, M., 2012. Synergistic antidiabetic activity of *Vernonia amygdalina* and *Azadirachta indica*: biochemical effects and possible mechanism. J Ethnopharmacol 141 (3), 878–887. doi:10.1016/j.jep.2012.03.041.

Awe, SO, Makindea, JM, Olajide, OA., 1999. Cathartic effect of the leaf extract of Vernonia amygdalina. Fitoterapia 70, 161–165. doi:10.1016/S0367-326X(99)00017-9.

Barnes, P, Yeboah, JK, Gbedema, W, Saahene, RO, Amoani, B., 2020. Ameliorative Effect of Vernonia amygdalina Plant Extract on Heavy Metal-Induced Liver and Kidney Dysfunction in Rats. Adv Pharmacol Pharm Sci doi:10.1155/2020/2976905.

Bihonegn, T, Giday, M, Yimer, G, Animut, A, Sisay, M., 2019. Antimalarial activity of hydromethanolic extract and its solvent fractions of *Vernonia amygdalina* leaves in mice infected with *Plasmodium berghei*. SAGE Open Med doi:10.1177/2050312119849766.

Cameron, KS, Howard, CB, Izevbigie, EB, Hill, BJ, Tchounwou, PB, 2013. Sensitivity and mechanisms of taxol-resistant prostate adenocarcinoma cells to Vernonia amygdalina extract. Exp Toxicol Pathol 65 (6), 759–765. doi:10.1016/j.etp.2012.11.002.

Challand, S, Willcox, M., 2009. A clinical trial of the traditional medicine Vernonia amygdalina in the treatment of uncomplicated malaria. J Altern Complement Med 15 (11), 1231–1237. doi:10.1089/acm.2009.0098.

Chukwuemeka, NO, Oyebisi, SO, Adebisi Oluwadare, OJ, Oladapo, RS, Berka, NP., 2018. Antibacterial assay and reversion of carbon tetrachloride induced liver damage on wistar mice by Vernonia amygdalina. Delile. Pak J Pharm Sci 31 (4), 1311–1321.

Chukwujekwu, JC, Lategan, CA, Smith, PJ, Van Heerden, FR, Van Staden, J., 2009. Antiplasmodial and cytotoxic activity of isolated sesquiterpene lactones from the acetone leaf extract of Vernonia colorata. S Afr J Bot 75 (1), 176–179. doi:10.1016/j.sajb.2008.10.001.

Dégbé, M, Debierre-Grockiego, F, Tété-Bénissan, A, Débare, H, Aklikokou, K, Dimier-Poisson, I, Gbeassor, M., 2018. Extracts of Tectona grandis and Vernonia amygdalina have anti-Toxoplasma and pro-inflammatory properties in vitro. Parasite 25, 11. doi:10.1051/parasite/2018014.

Degu, A, Kefale, B, Alemayehu, D, Tegegne, GT., 2020. Evaluation of the Antidiarrheal Activity of Hydromethanol Crude Extracts of Ruta chalepensis and Vernonia amygdalina in Mice. Evid Based Complement Alternat Med doi:10.1155/2020/8318713.

Dumas, NGE, Anderson, NTY, Godswill, NN, Thiruvengadam, M, Ana-Maria, G, Ramona, P, Crisan, GC, Laurian, V, Shariati, MA, Tokhtarov, Z, Emmanuel, Y., 2020. Secondary metabolite contents and antimicrobial activity of leaf extracts reveal genetic variability of Vernonia amygdalina and Vernonia calvoana morphotypes. Biotechnol Appl Biochem doi:10.1002/bab.2017.

Egedigwe, CA, Ijeh, II, Okafor, PN, Ejike, CE., 2016. Aqueous and methanol extracts of Vernonia amygdalina leaves exert their anti-obesity effects through the modulation of appetite-regulatory hormones. Pharm Biol 54 (12), 3232–3236. doi:10.1080/13880209.2016.1216135.

Ejike, CE, Awazie, SO, Nwangozi, PA, Godwin, CD., 2013. Synergistic postprandial blood glucose modulatory properties of Vernonia amygdalina (Del.), Gongronema latifolium (Benth.) and Occimum gratissimum (Linn.) aqueous decoctions. J Ethnopharmaco 149 (1), 111–116. doi:10.1016/j.jep.2013.06.009.

Erasto, P, Grierson, DS, Afolayan, AJ., 2006. Bioactive sesquiterpene lactones from the leaves of Vernonia amygdalina. J Ethnopharmacol 106 (1), 117–120. doi:10.1016/j.jep.2005.12.016.

Erukainure, OL, Chukwuma, CI, Sanni, O, Matsabisa, MG, Islam, MS, 2018. Histochemistry, phenolic content, antioxidant, and anti-diabetic activities of Vernonia amygdalina leaf extract. J Food Biochem doi:10.1111/jfbc.12737.

Erukainure, OL, Oyebode, OA, Ibeji, CU, Koorbanally, NA, Islam, MS., 2019. Vernonia Amygdalina Del. stimulated glucose uptake in brain tissues enhances antioxidative activities; and modulates functional chemistry and dysregulated metabolic pathways. Metab Brain Dis 34 (3), 721–732. doi:10.1007/s11011-018-0363-7.

Fachrunisa, D, Hasibuan, PAZ, Harahap, U., 2019. Cell Cycle Inhibition and Apoptotic Induction of *Vernonia amygdalina* Del. Leaves Extract on MCF-7 Cell Line. Open Access Maced J Med Sci 7 (22), 3807–3810. doi:10.3889/oamjms.2019.509.

Fadimu, OY, Iliya, M, Sani, RZ., 2014. Ethnomedicinal survey of anti-typhoid plants in ijebu ode local government area of Ogun state, Nigeria. Int J Sci Nat 5 (2), 332–336.

Gresham, LJ, Ross, J, Izevbigie, EB., 2008. Vernonia amygdalina: anticancer activity, authentication, and adulteration detection. Int J Environ Res Public Health 5 (5), 342–348. doi:10.3390/ijerph5050342.

Gudeta, BM, Taye, GM, Abula, T, Gadisa, AD, 2020. Evaluation of Anti-Diarrheal Activity of 80% Methanol Extracts of *Vernonia amygdalina* Delile (Asteraceae) Leaves in Mice. J Exp Pharmacol 5 (12), 455–462. doi:10.2147/JEP.S282669.

Habtamu, A, Melaku, Y., 2018. Antibacterial and Antioxidant Compounds from the Flower Extracts of Vernonia amygdalina. Adv Pharmacol Sci doi:10.1155/2018/4083736.

Hasibuan, P, Harahap, U, Sitorus, P, Satria, D., 2020. The anticancer activities of Vernonia amygdalina Delile. leaves on 4T1 breast cancer cells through phosphoinositide 3-kinase (PI3K) pathway. Heliyon 6 (7). doi:10.1016/j.heliyon.2020.e04449.

Howard, CB, McDowell, R, Feleke, K, Deer, E, Stamps, S, Thames, E, Singh, V, Pervin, S., 2016. Chemotherapeutic Vulnerability of Triple-negative Breast Cancer Cell-derived Tumors to Pretreatment with Vernonia amygdalina Aqueous Extracts. Anticancer Res 36 (8), 3933–3943.

IfedibaluChukwu, EI, Aparoop, D, Kamaruz, Z., 2020. Antidiabetic, anthelmintic and antioxidation properties of novel and new phytocompounds isolated from the methanolic stem-bark of Vernonia amygdalina Delile (Asteraceae). Scientific African 10. doi:10.1016/j.sciaf.2020.e00578.

Im, E, Ae, A, Bn, U, Po, U., 2016. Immuno-modulatory properties of prebiotics extracted from Vernonia amygdalina. Afr J Tradit Complement Altern Med 13 (6), 11–17. doi:10.21010/ajtcam.v13i6.3.

Imafidon, CE, Olukiran, OS, Ogundipe, DJ, Eluwole, AO, Adekunle, IA, Oke, GO, 2018. Acetonic extract of Vernonia amygdalina (Del.) attenuates Cd-induced liver injury: Potential application in adjuvant heavy metal therapy. Toxicology Reports 5, 324–332. doi:10.1016/j.toxrep.2018.02.009.

Iwalokun, BA, Efedede, BU, Alabi-Sofunde, JA, Oduala, T, Magbagbeola, OA, Akinwande, AI., 2006. Hepatoprotective and antioxidant activities of Vernonia amygdalina on acetaminophen-induced hepatic damage in mice. J Med Food 9 (4), 524–530. doi:10.1089/jmf.2006.9.524.

Iwalokun, BA., 2008. Enhanced antimalarial effects of chloroquine by aqueous Vernonia amygdalina leaf extract in mice infected with chloroquine resistant and sensitive Plasmodium berghei strains. Afr Health Sci 8 (1), 25–35.

Iwo, MI, Sjahlim, SL, Rahmawati, SF., 2017. Effect of Vernonia amygdalina del. leaf ethanolic extract on intoxicated male Wistar rats liver. Sci Pharm 85 (2), 16. doi:10.3390/scipharm85020016.

Jisaka, M, Ohigashi, H, Takegawa, K, Huffman, MA, Koshimizu, K., 2015. Antitumoral and antimicrobial activities of bitter sesquiterpene lactones of Vernonia amygdalina, a possible medicinal plant used by wild chimpanzees. Biosci Biotechnol Biochem 57 (5), 833–834. doi:10.1271/bbb.57.833.

Johnson, W, Tchounwou, PB, Yedjou, CG., 2017. Therapeutic Mechanisms of Vernonia amygdalina Delile in the Treatment of Prostate Cancer. Molecules 22 (10), 1594. doi:10.3390/molecules22101594.

Koshimizu, K, Ohigashi, H, Huffman, MA., 1994. Use of Vernonia amygdalina by wild chimpanzee: possible roles of its bitter and related constituents. Physiology and behavior 56 (6), 1209–1216. doi:10.1016/0031-9384(94)90368-9.

Liu, H, Kang, P, Liu, Y, An, Y, Hu, Y, Jin, X, Cao, X, Qi, Y, Ramesh, T, Wang, X., 2020. Zinc oxide nanoparticles synthesised from the Vernonia amygdalina shows the anti-

inflammatory and antinociceptive activities in the mice model. Artif Cells Nanomed Biotechnol 48 (1), 1068–1078. doi:10.1080/21691401.2020.

Lolodi, O, Eriyamremu, GE., 2013. Effect of methanolic extract of Vernonia amygdalina (common bitter leaf) on lipid peroxidation and antioxidant enzymes in rats exposed to cycasin. Pak J Biol Sci 16 (13), 642–646. doi:10.3923/pjbs.2013.642.646.

Luo, X, Jiang, Y, Fronczek, FR, Lin, C, Izevbigie, EB, Lee, KS., 2011. Isolation and structure determination of a sesquiterpene lactone (vernodalinol) from Vernonia amygdalina extracts. Pharm Biol 49 (5), 464–470. doi:10.3109/13880209.2010.523429.

Masaba, SC., 2000. The antimalarial activity of Vernonia amygdalina Del (Compositae). Trans R Soc Trop Med Hyg 94 (6), 694–695. doi:10.1016/s0035-9203(00)90236-0.

Michael, UA, David, BU, Theophine, CO, Philip, FU, Ogochukwu, AM, Benson, VA., 2010. Antidiabetic effect of combined aqueous leaf extract of Vernonia amygdalina and metformin in rats. J Basic Clin Pharm 1 (3), 197–202.

Momoh, MA, Muhamed, U, Agboke, AA, Akpabio, EI, Osonwa, UE., 2012. Immunological effect of aqueous extract of Vernonia amygdalina and a known immune booster called immunace(®) and their admixtures on HIV/AIDS clients: a comparative study. Asian Pac J Trop Biomed 2 (3), 181–184. doi:10.1016/S2221-1691(12)60038-0.

Nagy, N, Kuipers, HF, Frymoyer, AR, Ishak, HD, Bollyky, JB, Wight, TN, Bollyky, PL., 2015. 4-methylumbelliferone treatment and hyaluronan inhibition as a therapeutic strategy in inflammation, autoimmunity, and cancer. Front Immunol 6, 123. doi:10.3389/fimmu.2015.00123.

Ngatu, NR, Okajima, MK, Yokogawa, M, Hirota, R, Takaishi, M, Eitoku, M, Muzembo, BA, Sabah, AB, Saruta, T, Miyamura, M, Kaneko, T, Sano, S, Suganuma, N., 2012. Anti-allergic effects of Vernonia amygdalina leaf extracts in hapten-induced atopic dermatitis-like disease in mice. Allergol Int 61 (4), 597–607. doi:10.2332/allergolint.11-OA-0393.

Nguyen, TXT, Dang, DL, Ngo, VQ, Trinh, TC, Trinh, QN, Do, TD, Thanh, TTT., 2020. Anti-inflammatory activity of a new compound from Vernonia amygdalina. Nat Prod Res 1–6. doi:10.1080/14786419.2020.1788556.

Njan, AA, Adzu, B, Agaba, AG, Byarugaba, D, Díaz-Llera, S, Bangsberg, DR, 2008. The analgesic and antiplasmodial activities and toxicology of Vernonia amygdalina. J Med Food 11 (3), 574–581. doi:10.1089/jmf.2007.0511.

Ohigashi, H, Huffman, MA, Izutsu, D, Koshimizu, K, Kawanaka, M, Sugiyama, H, Kirby, GC, Warhurst, DC, Allen, D, Wright, CW, Phillipson, JD, Timon-David, P, Delmas, F, Elias, R, Balansard, G., 1994. Toward the chemical ecology of medicinal plant use in chimpanzees: The case of Vernonia amygdalina, a plant used by wild chimpanzees possibly for parasite-related diseases. J Chem Ecol 20, 541–553. doi:10.1007/BF02059596.

Okon, UA, Umoren, IU., 2017. Comparison of antioxidant activity of insulin, Ocimum gratissimum L., and Vernonia amygdalina L. in type 1 diabetic rat model. J Integr Med 15 (4), 302–309. doi:10.1016/S2095-4964(17)60332-7.

Opata, MM, Izevbigie, EB., 2006. Aqueous Vernomia amygdalina extracts alter MCF-7 cell membrane permeability and efflux. Int J Environ Res Public Health 3 (2), 174–179. doi:10.3390/ijerph2006030019.

Okpe, O, Habila, N, Ikwebe, J, Upev, VA, Okoduwa, SI, Isaac, OT, 2016. Antimalarial Potential of Carica papaya and Vernonia amygdalina in Mice Infected with Plasmodium berghei. J Trop Med doi:10.1155/2016/8738972.

Okoduwa, SIR, Umar, IA, James, DB, Inuwa, HM, Habila, JD, Venditti, A., 2020. Bioguided fractionation of hypoglycaemic component in methanol extract of Vernonia amygdalina: an in vivo study. Nat Prod Res 13, 1–5. doi:10.1080/14786419.2020.1805605.

Oladele, JO, Oyeleke, OM, Oladele, OT, Olaniyan, M., 2020. Neuroprotective mechanism of *Vernonia amygdalina* in a rat model of neurodegenerative diseases. Toxicol Rep 14 (7), 1223–1232. doi:10.1016/j.toxrep.2020.09.005.

Omojokun, OS, Famurewa, AJ, Jaiyeoba, OA, Oboh, G, Agbebi, OJ., 2019. Alkaloid extracts from Bitter leaf (Vernonia amygdalina) and Black nightshade (Solanum nigrum) inhibit phosphodiesterase-5, arginase activities and oxidative stress in rats penile tissue. J Food Biochem. doi:10.1111/jfbc.12889.

Omoregie, ES, Pal, A., 2016. Antiplasmodial, antioxidant and immunomodulatory activities of ethanol extract of Vernonia amygdalina del. Leaf in Swiss mice. Avicenna J Phytomed 6 (2), 236–247.

Onasanwo, SA, Oyebanjo, OT, Ajayi, AM, Olubori, MA, 2017. Anti-nociceptive and anti-inflammatory potentials of *Vernoniaamygdalina* leaf extract via reductions of leucocyte migration and lipid peroxidation. J Intercult Ethnopharmacol 6 (2), 192–198. doi:10.5455/jice.20170330010610.

Ong, KW, Hsu, A, Song, L, Huang, D, Tan, BK., 2011. Polyphenols-rich Vernonia amygdalina shows anti-diabetic effects in streptozotocin-induced diabetic rats. J Ethnopharmacol 133 (2), 598–607. doi:10.1016/j.jep.

Owolabi, MA, Jaja, SI, Olatunji, OJ, Oyekanmi, OO, Adepoju, S., 2011. Attenuation of oxidative damage in alloxan induced diabetic rabbits following administration of the extract of the leaves of Vernonia amygdalina. Free Radicals and Antioxidants 1 (3), 93–101.

Oyeyemi, IT, Aderiike, AA, Adewumi, A, Aleshinloye, AO, Oyeyemi, OT., 2018. *Vernonia amygdalina*: A folkloric herb with anthelminthic properties. Beni-Suef Uni J Basic Applied Sci J 43–49. doi:10.1016/j.bjbas.2017.07.007.

Shittu, OB, Ajayi, OL, Bankole, SO, Popoola, TO., 2016. Intestinal ameliorative effects of traditional Ogi-tutu, Vernonia amygdalina and Psidium guajava in mice infected with Vibrio cholera. Afr Health Sci 16 (2), 620–628 10.4314/ahs.v16i2.33.

Sinisi, A, Millán, E, Abay, SM, Habluetzel, A, Appendino, G, Muñoz, E, Taglialatela-Scafati, O., 2015. Poly-Electrophilic Sesquiterpene Lactones from Vernonia amygdalina: new members and differences in their mechanism of thiol trapping and in bioactivity. J Nat Prod 78 (7), 1618–1623. doi:10.1021/acs.jnatprod.5b00179.

Song, YS, Park, CM., 2014. Luteolin and luteolin-7-O-glucoside strengthen antioxidative potential through the modulation of Nrf2/MAPK mediated HO-1 signaling cascade in RAW 264.7 cells. Food Chem Toxicol 65, 70–75. doi:10.1016/j.fct.2013.12.017.

Tekou, FA, Kuate, D, Nguekouo, PT, Woumbo, CY, Oben, JE., 2018. Effect of cooking treatments on the phytochemical composition and antidiabetic potential of *Vernonia amygdalina*. Food Sci Nutr 6 (6), 1684–1691. doi:10.1002/fsn3.732.

Toyang, NJ, Verpoorte, R., 2013. A review of the medicinal potentials of plants of the genus Vernonia (Asteraceae). J Ethnopharmacol 146 (3), 681–723. doi:10.1016/j.jep.2013.01.040.

Ugbaja, RN, Akinhanmi, TF, James, AS, Ugwor, EI, Babalola, AA, Ezenandu, EO, Ugbaja, VC, Emmanuel, EA, 2021. Flavonoid-rich fractions from Clerodendrum volubile and Vernonia amygdalina extenuates arsenic-invoked hepatorenal toxicity via augmentation of the antioxidant system in rats. Clinical Nutrition Open Science 35, 12–25. doi:10.1016/j.nutos.2020.12.003.

Wang, J, Song, H, Wu, X, Zhang, S, Gao, X, Li, F, Zhu, X, Chen, Q, 2018. Steroidal Saponins from Vernonia amygdalina Del. and Their Biological Activity. Molecules 23 (3), 579. doi:10.3390/molecules23030579.

Wong, FC, Woo, CC, Hsu, A, Tan, BK., 2013. The anti-cancer activities of Vernonia amygdalina extract in human breast cancer cell lines are mediated through caspase-dependent and p53-independent pathways. PLoS One doi:10.1371/journal.pone.0078021.

Wu, XM, Ren, T, Liu, JF, Liu, YJ, Yang, LC, Jin, X, 2018. Vernonia amygdalina Delile extract inhibits the hepatic gluconeogenesis through the activation of adenosine-5′monophosph kinase. Biomed Pharmacother 103, 1384–1391. doi:10.1016/j.biopha.2018.04.135.

Yedjou, CG, Izevbigie, EB, Tchounwou, PB., 2013. Vernonia amygdalina-induced growth arrest and apoptosis of breast cancer (MCF-7) cells. Pharmacol Pharm doi:10.4236/pp.2013.41013.

Yedjou, CG, Sims, JN, Njiki, S, Tsabang, N, Ogungbe, IV, Tchounwou, PB., 2018. Vernonia amygdalina delile exhibits a potential for the treatment of acute promyelocytic leukemia. Glob J Adv Eng Technol Sci 5 (8), 1–9. doi:10.5281/zenodo.134359.1.

Yeshanew, S, Gete, W, Chilo, D., 2021. Evaluation of the Antimalarial Activity of Ethanol Extracts of the Leaves of Three Plant Species Collected from Yayu Coffee Forest Biosphere Reserve, Southwest Ethiopia. J Exp Pharmacol 13, 661–668. doi:10.2147/JEP.S304933.

Yusoff, SF, Haron, FF, Mohamed, TMM, Asib, N, Sakimin, SZ, Kassim, Abu, F, Ismail SI., 2020. Antifungal Activity and Phytochemical Screening of Vernonia amygdalina Extract against Botrytis cinerea Causing Gray Mold Disease on Tomato Fruits. Biology 9 (9), 286. doi:10.3390/biology9090286.