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Review Article

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A review: secondary metabolites of *Uvaria chamae* p. Beauv. (Annonaceae) and their biological activities

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Abstract

Uvaria chamae p. Beauv., synthesizes and accumulates a variety of secondary metabolites from its root, stem, leaf and fruit. These consist mainly of essential oils, flavonoids, alkaloids and annonaceous acetogenins. Some of these biologically active secondary metabolites validate the claim made in traditional system of medicine. The present review summarizes the information available on the secondary metabolites isolated from *U. chamae* and their biological activities.

Keywords: Secondary metabolites, Essential oils, Flavonoids, alkaloids, Annonaceous acetogenins

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Introduction

The primary metabolites are of major importance to plants, while the secondary metabolites are of medicinal value to man (Trease and Evans, 1989) and these can equally be obtained from various anatomical structures of plants (Fahn, 1974). Man has benefited from the presence of these chemicals by exploiting the plant products as sources of sustenance in a variety of ways. For example, many drugs today are of plant origin. Pharmacological history is abounding with examples such as quinine, aspirin, picrotoxin, reserpine etc., while many of the synthetic drugs are fashioned after natural plant products (Sofowora, 1982).

The Annonaceae is a large family of shrubby aromatic plants composed of 112 genera with about 2,150 species (Mabberly, 1997) and grows to about 3.6 m to 4.5 m tall. *Uvaria chamae* P. Beauv., commonly known as "finger root" is a climbing shrub and is found in the tropical wet and dry forests of west and central Africa along coastal scrubland. It is found alongside water in marsh forest with *Alchornea cordifolia*, *Thalia* (Maranthaceae), *Dracaena arborea*, *Cyrtosperma*, *Anthocleista vogeliana*, *ferns*, *Mussa endaiserteana*, *Mitragyna stipulosa*, *Cyclosaurus* (Arbonnier, 2004; Bongers et al., 2005). The fruit carpel's are in finger-like clusters, the shape giving rise to many vernacular names translated as "bush banana" or the like implying wildness where in Igala is called Ayiloko, Hausa: Kaskaifi, Yoruba: Okooja and Ghana: Akotompo. The fruits are yellow when ripe and have a sweet pulp which are edible and widely eaten (Iwu, 1993). *Uvaria chamae* is an important medicinal plant. The secondary metabolites isolated from the plant and their biological activities are reviewed.

Chemical Constituents

The search for the concerned active compounds has led to isolation of the several flavonoids, alkaloids, annonaceous acetogenins and essential oils from different plant parts of *U. chamae*. The preliminary phytochemicals detected from different parts of the plant are listed in Table 1 which shows the phytochemical groups present or absent in different plant parts. The bioactive compounds present in the essential oils and flavonoids isolated from the plant are listed in Table 2 and 3.

Scientific classification

Kingdom:	Plantae
(unranked):	Angiosperms
(unranked):	Magnoliids
Order:	Magnoliales
Family:	Annonaceae
Genus:	*Uvaria*
Species:	*chamae*

Essential oils

The essential oil from the root bark and leaves of *U. chamae* showed the presence of different constituents (Table 2). The oil from the root contained a number of oxygenated benzylbenzoate derivatives and ethers. The oil from the leaf contains predominantly sesquiterpene hydrocarbons, oxygenated sesquiterpenes, monoterpene hydrocarbons as well as oxygenated ones (Ayedoun et al., 1999). Thymoquinoldimethyl ether, benzyl benzoate, chamanen, o-methoxybenzylbenzoate, o-methoxybenzyl benzyl ether, and di-o-methoxybenxyl ether are the major components of the root oil (Park and Sutherland, 1969; Lasswell and Hufford, 1977a) while the oil from the leaf was dominated by 1-nitro-2-phenylethane (63.2%), linalool (9.9%), and germacrene D (6.6%) (Moses et al., 2013) as shown in Table 2. The bioactivities of the major constituents account for the traditional uses of *U. chamae* leaves and roots to treat fevers, wounds, swellings, injuries, etc.

Flavonoids

Since 1976, flavonoids of a special type have been obtained from several *Uvaria chamae*. These are the novel

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C-benzylated flavanones and C-benzylated dihydrochalcones as shown in Table 3. Some of them have demonstrated cytotoxic, antitumor and antimicrobial properties. Although flavanones and chalcones are widespread in higher plants, the introduction of benzyl groups is quite rare and seems to be limited to *Uvaria chamae* (Bindu, 1998).

Annonaceous Acetogenins

Annonaceous Acetogenins are a unique class of C-35 or C37 secondary metabolites derived from long chain (C-32 or C34) fatty acids in the polyketide pathway. They are usually characterized by a combination of fatty acids with a 2-propanol unit at C-2 that forms a methyl-substituted α,β-unsaturated γ-lactone (Alali et al., 1999). Since the discovery of uvaricin from *Uvaria accuminata* in 1982, more than 500 acetogenins have been identified from different parts of the plants in the Annonaceae family (Tempesta et al., 1982; McLaughlin, 2008) and over 400 members of this family of compounds have been isolated from 51 different species of plants (Bermejo et al., 2005). Due to the special structures and extensive biological activities, Acetogenins have attracted significant scientific interest in recent years.

Various biological activities have been reported for Acetogenins, including antimalarial, antiparasitic and pesticidal activities (Zafra-Polo et al., 1998; Alali et al., 1999). However, the biological activities of AGEs are primarily characterized with toxicity against cancer cells and inhibitory effects against the mitochondrial complex I (mitochondrial NADH: ubiquinone oxido-reductase) (Zafra-Polo et al., 1996; Chih et al., 2001). However, new adjacent bis –tetrahydrofuran annonaceous acetogenin, joolanin, along with eight known acetogenins, squamocin, desacetyluvaricin, chamuvarinin, tripoxyrollin, dieporeticanin-1, dieporeticanin-2 and dieporeticenin were isolated from the seeds of *Uvaria chamae*. Joolanin has been shown to exhibit cytotoxicity effect towards the KB 3-1 cell line (IC_{50}) =0.4 nM (Fall et al., 2004). Also, cis-bullatencin, bullatencin, annotemoyin-1, solamin, uvariamicin-I, -II, -III, cis-reticulatacin and cis-uvariamicin-I (Fall, 2002) and chamuvarinin (Fall et al., 2004) was also isolated from the root of *U. chamae*.

Alkaloids

Philipov and co-workers in 2000 carried out a study on the phytochemical evaluation of leaves of *Uvaria chamae* which resulted in the isolation for the first time for the genus of *Uvaria* of benzylisoquinoline alkaloids (+)-armepavine and racem O, O-dimethyl coclaurine. The aporphines nornantenine, nantenine and corydine are new for the species.

Ethnopharmacology

All parts of *Uvaria chamae* are fragrant. The root-bark yields an oleo-resin and is taken internally for catarrhal inflammation of mucous membranes, bronchitis and gonorrhoea in Nigeria (AkéAssi et al., 1985), while at one time a fluid extract entered into the composition of a stock hospital prescription in Ghana for dysentery (Marshall et al., 2000). The properties are mainly astringent and styptic, and it is used in native medicine as a specific for piles, useful also for menorrhagia (for which it is taken mixed with Guinea grains and added to food), epistaxis, haematuria, hematemesis and haemoptysis. In Sierra Leone, the root is credited with having purgative and febrifugal properties (Ayedoun et al., 1999; Burkill, 2000; Igoli et al., 2005). In Sierra Leone the root or the root-bark is boiled with spices and the decoction drunk for fevers classed locally as 'yellow-fever', including almost any indisposition accompanied by jaundice (Ayedoun et al., 1999; Burkill, 2000), and in the Ivory Coast it enters into a treatment for a form of jaundice (Arbonnier, 2000). In the Casamance of Senegal, leaves and roots are macerated for internal use as a cough mixture (Burkill, 2004), and mixed with those of *Annona senegalensis*, dried and pulverized are considered strong medicine for renal and costal pain (Madubunyi et al., 1996). The roots are used in the Casamance for healing sores, and a concoction called n'taba in the Bayot dialect is reputed to cure infantile rickets. In Nigeria a root-decoction is also held to be stomachic and vermifugal, and is used as a lotion; sap from the root and stem is applied to wounds; used for the treatment of nose bleeding, heart diseases (bronchi, lungs etc.), and blood in urine, pile and fever (Adams and Moss, 1999; Etukudo, 2003). The root is made into a drink and a body-wash for oedematous conditions (Ayedoun et al., 1999). Its root-decoction is given for the pains of childbirth in Togo (Oguntimein et al., 1989; Nwosu, 2000).

Table 1. The preliminary phytochemicals present in different parts of *Uvaria chamae*

		Plant parts			
S/No.	**Chemical classes**	**Root**	**Stem Bark**	**Leaves**	**Fruit/seeds**
1.0	Alkaloids	+	-	+	NPD
2.0	Glycosides	-	+	NPD+	NPD
3.0	Saponins	-	+	+	,,
4.0	Tannins	+	+	+	,,
5.0	Flavonoids	+	+	+	+
6.0	Reducing sugar	+	+	-	NPD
7.0	Quinonic derivatives	+	NPD	NPD	,,
8.0	Leucoanthocyanes	+	NPD	,,	,,
9.0	Terpenes/Terpenoids	+	,,	+	,,
10	Essentials oils	+	,,	+	,,
References		Thierry et al., 2012; Emordi et al., 2015	Ebia et al., 1999; Oluremi et al., 2010	Borokini and Omotayo, 2012; Moukimou et al., 2014	Basil, 2017

+: Present, -: Absent, NPD: No published data

Table 2. Chemical Composition of *Uvaria chamae* Leaf and Root Essential Oil

S/No.	Compounds	%	S/No.	Compounds	%
1.0	α-Pinene	0.3	38	Thymoquinoldimethyl ether	-
2.0	β-Pinene	0.2	39	Alloaromadendrene	0.1
3.0	Camphene	Trace	40	*cis*-Cadina-1(6),4-diene	Trace
4.0	Benzaldehyde	Trace	41	*trans*-Cadina-1(6),4-diene	0.1
5.0	Myrcene	0.2	42	γ-Muurolene	0.2
6.0	α-Phellandrene	Trace	43	Germacrene D	6.6
7.0	δ-3-Carene	Trace	44	β-Selinene	1.0
8.0	a-Terpinene	Trace	45	*trans*-Muurola-4(14),5-diene	0.3
9.0	*p*-Cymene	0.4	46	*epi*-Cubebol	0.7
10	Limonene	0.1	47	Bicyclogermacrene	0.3
11	1,8-Cineole	0.6	48	α-Muurolene	0.3
12	(*Z*)-b-Ocimene	0.1	49	Germacrene A	0.2
13	(*E*)-b-Ocimene	1.9	50	(*E,E*)-α-Farnesene	0.1
14	γ-Terpinene	0.2	51	Cubebol	0.8
15	Linalool	9.9	52	δ-Cadinene	2.1
16	Benzeneacetonitrile	0.1	53	*trans*-Cadina-1,4-diene	0.1
17	(*E*)-Epoxyocimene	Trace	54	α-Cadinene	Trace
18	Borneol	0.1	55	Elemol	0.1
19	Terpinen-4-ol	Trace	56	Germacrene B	Trace
20	α-Terpineol	0.1	57	(*E*)-Nerolidol	1.4
21	(3*Z*)-Hexenyl 2-methylbutanoate	Trace	58	(3*Z*)-Hexenyl benzoate	0.2
22	Bornyl acetate	Trace	59	Spathulenol	0.2
23	1-Nitro-2-phenylethane 63.2	63.2	60	Caryophyllene oxide	0.3
24	(3*Z*)-Hexenyltiglate	0.1	61	Gleenol	Trace
25	α-Cubebene	0.2	62	Humulene epoxide II	0.1
26	α-Copaene	0.4	63	1-*epi*-Cubenol	0.4
27	β-Bourbonene	0.2	64	τ-Cadinol	Trace
28	β-Cubebene	0.2	65	τ-Muurolol	0.7
29	β-Elemene	0.2	66	α-Muurolol (= Torreyol)	0.2
30	(*E*)-Caryophyllene	1.7	67	α-Cadinol	0.5
31	β-Copaene	0.1	68	Pentadecanal	0.1
32	α-*trans*-Bergamotene	0.1	69	Benzyl benzoate	0.9
33	6,9-Guaiadiene	Trace	70	Palmitic acid	0.2
34	*cis*-Muurola-3,5-diene	0.1	71	(*E*)-Phytol	0.1
35	α-Humulene	0.6	72	o-methoxybenzylbenzoate	-
36	(*E*)-β-Farnesene	0.2	73	o-methoxybenzyl benzyl ether	-
37	chamanen	-	74	di-o-methoxybenzyl ether	-

Table 3. Chemical Composition of *Uvaria chamae* Stem and Root bark C-benzylated Flavonoids

S/No.	Compounds	Plant part	References
1.0	Pinocembrin	Stem, Root	Hufford and Lasswell, 1976
2.0	Pinostrobin	Stem, Root	Hufford and Oguntimein, 1980
3.0	Chamanetin	Root	Hufford and Lasswell, 1976; Lasswell and Hufford, 1977, Hufford et al., 1980; Hufford and Oguntimein, 1980
4.0	Chamanetin 5-methylether	Root	Hufford and Lasswell, 1976, El-Soly et al., 1979
5.0	Isochamanetin	Root	Hufford and Lasswell, 1976
6.0	Uvaretin	Stem, Root	Okorie, 1977; Nkunya et al., 1985
7.0	Isouvaretin	Stem, Root	Hufford et al., 1980; Nkunya et al., 1985
8.0	Dichamanetin	Root	Hufford and Lasswell, 1976; Lasswell and Hufford, 1977
9.0	Dichamanetin-5-methylether	Root	Hufford and Lasswell, 1976; Lasswell and Hufford, 1977
10	Diuvaretin	Stem, Root	Okorie, 1977; Nkunya et al., 1993
11	Chamuvaritin	Root	Hufford et al., 1979; Derbre´ et al., 2004; Fall et al., 2004; Laurens et al., 2004
12	Uvarinol	Stem, Root	Hufford et al., 1979

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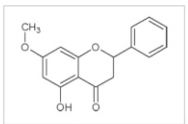
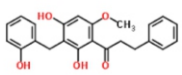
Table 4. Biological activities for extracts of *Uvaria chamae*

S/No.	Extract	Plant part	Country	IC_{50}/ED_{50} conc. used	Species	Ref.
1.0	Antidiabetic & hypolipidemic activity 93.3% aqueous ethanol ext.	Root	Nigeria	100 mg/kg 250 mg/kg 400 mg/kg	Rat	Emordi et al. 2016
2.0	Hypoglycaemic activity 93.3% aqueous ethanol ext.	Root	Nigeria	250 mg/kg 500 mg/kg	Rat	Emordi et al. 2015
3.0	Anti-inflammatory activity ethanol ext.	Root	Nigeria	25 mg/kg 150 mg/kg	Mouse Rat	Okwu et al., 2009.
4.0	Oxytocic activity ethanol ext.	Root	Nigeria	15 mg/100 mL	Guinea pig	Okwu et al., 2009.
5.0	Antioxidant activity 1. Ethanol, acetone (AcE), 2. aqueous (AqE) extracts	1. Leaves 2. Seed	Nigeria ,,	1. 2-50 µg/mL 2. 1 mL	1,1-diphenyl-2-picrylhydrazyl (DPPH)	Moukimou et al., 2014; Basil, 2017.
6.0	Anti-malarial activity 1. Ethanol ext. 2. aqueous extracts	Leaf, stem bark, and root	Nigeria	100 mg/kg	*Plasmodium berghei* NK 65	Ene et al., 2016
7.0	Antibacterial activity 1. 70% ethanol ext., aqueous ext. 2. Methanol ext.	1. Root 2. Root, stem & leaf	1. Côte d'Ivoire 2. Nigeria	1. 3.125 to 100 mg/ml. 2. 50, 100, 150, 200 & 250 mg/ml	1. *E. c.*s, *E.c.*E., *S.f.*E and *S.*sp 2. MRSA, S.a, E.c, *K.*spp, *P.* spp, strains of *E.c*, *S.a*, *P.a*	Kone et al., 2015; Oluremiet al., 2010
8.0	Hepatoprotective activity Methanol extract	Root bark	Nigeria	60 mg/kg	Rats	Madubunyi, 2012
9.0	Antihaemolytic activity Water extract	Root bark	Nigeria	5 mg/mL	Red blood cells	Thierry et al., 2012
10	Genotoxic activity Methanol extract	Leaf	Nigeria	125, 250, 750 mg/kg	Mouse	Awodiran et al., 2017

*E.c.s: Escherichia coli*soluble; *E.c.*E: *Escherichia coli* ESBL; *S.f.*E: *Shigella. Flexneri* ESBL; *S*: *Shigella*:; MRSA: Methicillin-Resistant *Staphylococcus aureus*; *S.a*: *Staphylococcus aureus*; *K*: *Klebsiella*; *P*: *Proteus*; *P.a*: *Pseudomonas aeruginosa*


Pinostrobin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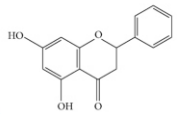
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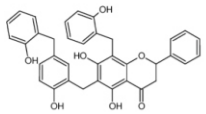
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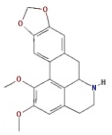
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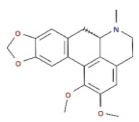
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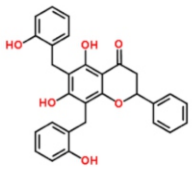
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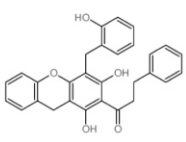
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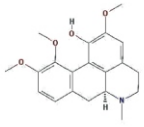
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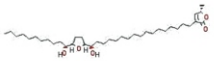
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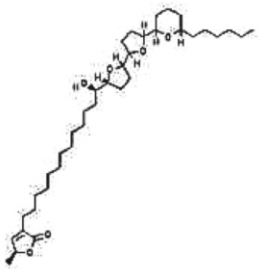
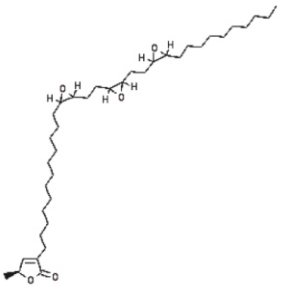


Chamuvarinin



Tripoxyrollin

Biological Activities

Antidiabetic activity

Emordi et al. 2016 evaluated the antidiabetic effect of *Uvaria chamae* extract in rat. The effects of the extract on weight, plasma glucose and other biochemical parameters were evaluated using standard procedures. The diabetic rats treated with the extract showed significant reductions ($p < 0.05$) in weight, plasma glucose levels, low density lipoprotein and cholesterol compared with the control. The extract showed maximum glucose reduction of 85.16, 81.50 and 86.02% respectively. Histologically the pancreas of the diabetic rats treated with the extract, showed clusters of variably sized regenerated islet of Langerhans within sheets of normal exocrine pancreas, while the pancreas of diabetic rats treated with insulin showed no islet of Langerhans. These activities of the extract may be accounted for by the presence of several bioactive compounds like flavonoids, tannins and alkaloids. Suba et al., 2004 reported that tannin has antidiabetic activity. Research has shown that many plants containing flavonoids have been used for the treatment of diabetes (Meiselman et al., 1976; Choi et al., 1991; Hassig et al., 1999). Tannins induce phosphorylation of the insulin receptors as well as translocation of glucose transporters 4 (GLUT-4) , the protein factor involved in the signaling pathway of insulin-mediated glucose transport and the inhibition of the expression of key gene for adipogenesis thereby helping to reduce blood glucose level without increasing adiposity (Liu et al., 2005).

Antimicrobial activity

Studies have shown that Pinocembrin can significantly inhibit the activity of *Penicillium italicum* (Sala et al., 2003), *Candida albicans* (Metzner and Schneidewind, 1978; Katerere et al., 2012), *Staphylococcus aureus* (Soromou et al., 2013), *E. coli* (Katerere et al., 2012), *Bacillus subtilis*, *Trichophyton mentagrophytes*, *Streptococcus mutans* (Uzel et al., 2005) and *Neisseria gonorrhoeae* (Ruddock et al., 2011). More so, the antimicrobial activities of a number of cytotoxic C-benzylatedflavanones (Flavonoids) namely chamanetin, isochamanetin and dichamanetin from *Uvaria chamae* root bark ethanol extracts were also determined. The minimum inhibitory concentration values of these compounds and certain of their derivatives against *Streptococcus aureus*, *Bacillus subtilis* and *Mycobacterium smegmatis* compare favorably with those of streptomycin sulphate (Anam et al., 1993; Achenbach et al., 1997). Alkaloids are also significantly recognized for their antimicrobial properties (Manikandan et al., 2006; Mariita et al., 2011), and they might play a role in disease resistance (Salisbury and Ross, 1992). In addition, linalool has shown antimicrobial activities (Peana et al., 2003), which is present in the leaf extract of *U. chamae*.

Anti-inflammatory and oxytocic activity

The anti-inflammatory and oxytocic properties of *U. chamae* root ethanol extract were assessed. The extracts and aspirin were found to inhibit carrageenan-induced paw oedema on albino rats and mice with a strong activity in aspirin having (80.43 %) inhibition while *U. chamae* had 69.57% inhibition respectively. In the oxytoxic property assessment, uterus from young virgin guinea pig was used. The plant extract exhibited more uterine contraction in the guinea pig which was comparable to that of oxytocin (Okwu et al., 2009). 1-Nitro-2-phenylethane and linalool had shown anti-inflammatory effect (Peana et al., 2002; De Lima, 2008). Flavonoids possessed the highest phytochemical content in this study which may be responsible for the above activities. However, Pinocembrin has been shown in *in vitro* studies to inhibit proinflammatory cytokines in the murine macrophage and endotoxin-induced acute lung injury model, partly by decreasing the levels of MAPK and NF-kB activation. More so, *in vivo* studies also showed that pretreatment with pinocembrin (intraperitoneal, 50 mg/kg) attenuated inflammation and reduced lung injury in a murine model of lipopolysaccharide (LPS)-induced inflammation (Soromou et al., 2012).

Furthermore, the anti-inflammatory effect of *Uvaria chamae* methanol extract on acetic acid- induced acute colitis in rats identified from a previous ethnobotanical study was evaluated. Acetic acid was diluted in normal saline to be 4% and infused into the colon of rats through a rubber cannula at the dose of 4 mL/kg. 50 – 400 mg/kg and 2 mg/kg of prednisolone (standard drug) was orally administered 48, 24 and 1 hour prior to the induction of colitis and continued for 1 week. The extract doses (50-400mg/kg) significantly reduced the macroscopic inflammation scores and morphological alterations associated with an increase in the mucus secretion ($p<0.05$) with no significant difference among the treatment groups which indicated its effectiveness at all levels of doses in the treatment of ulcerative colitis (Abu et al., 2018).

Cytotoxicity Activity

The MTT (3-(4, 5-dimethyl thiazole-2-yl)-2, 5-diphenyl-tetrazolium bromide) colorimetric assay was used to

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determine the cytotoxic concentration of extracts/ fractions at 50% (CC_{50}) with ten-fold serial dilution (100 to 0.001 µg/mL) of each extract treatment. The methanol crude extract of *Uvaria chamae* root bark was most toxic with CC50 of 15.90 µg/mL, while *Uvaria chamae* stem bark was least toxic with CC50 of 38.92 µg/mL. The methanol fraction from *Uvaria chamae* stem bark was more toxic than its other fractions with CC50value of 23.01 µg/mL, while hexane, dichloromethane, and ethylacetate fractions and the crude extract have similar cytotoxic activity pattern with CC50 values of 39.10 µg/mL, 38.95µg/mL, 38.15 µg/mL and 38.92 µg/mL respectively (Oluremi and Adeniji, 2015). Recently, Awodiran et al., 2017, assessed the cytotoxicity properties of methanol *U. chamae* leaves extract by using mitotic index determinant and found to exhibit dose-dependent cytotoxicity at doses of 125, 250, and 750 mg/kg/day comparable to the standard, Cyclophosphamide (50 mg/kg, single dose).More so, ethanol extract of the stem bark of *U. chamae* was found to show activity *in vivo* against P-388 leukemia in the mouse and *in vitro* against cells derived from human carcinoma of the nasopharynx (KB). Fractionation of the ethanol extract was guided by assay against carcinoma of the nasopharynx (KB). The activity was concentrated in the ethyl acetate soluble fraction of an ethylacetate-water partition. Chromatography of the ethyl acetate fraction over salicylic acid gave uvaretin and isouvaretin (Hufford and Lasswell, 1976). In addition, the isolation and characterization of three novel C-benzylated flavanones, chamanetin, isochamanetin, and dichamanetin and three C-benzylated dihydro-chalcones, uvaretin, isouvaretin and diuvaretin from ethanol extracts of the root bark of *U. chamae* also showed to be responsible for its cytotoxic effect (Hufford and Lasswell, 1976; Lasswell and Hufford, 1977). Chamuvarinin has also showed significant cytotoxicity toward KB 3-1 cervix cancer cell lines (IC_{50}) 0.8 nM) (Derbre´ et al., 2004; Fall et al., 2004).

The aforementioned alkaloids were found to express cytotoxic activity against L929 transformed cells. The highest activity was shown by (+)-armepavine and nornantenine (Philipov et al., 2000).

Antioxidant activity

The antioxidant activity of seed extracts of *Uvaria chamae* was investigated by measuring its DPPH (1, 1-diphenyl-2-picrylhydrazyl), ABTS (2, 2-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid) scavenging activities and its metal chelating and ferric reducing potentials. In addition, total phenolic and flavonoid content of the seed extracts was evaluated. The seed extracts exhibited potent antioxidant activity in the DPPH and ABTS assay, with the ethanol seed extract of *Uvaria chamae* being more effective (IC_{50} = 34.3 and 29.6 µg/mL respectively). However, the aqueous seed extract of *Uvaria chamae* exhibited the highest metal chelating activity (IC_{50}= 23.5 µg/mL), while its ethanol extract showed higher reducing power than the standard. In addition, high content of phenolics and flavonoids was found in the organic seed extracts (Basil, 2017). Flavonoids are a group of phytochemicals that have been shown to exert potent anti-oxidant activity against the superoxide radical (Hertog et al., 1993). Hence, Pinocembrin, a natural flavonoid compound which has also been extracted from other source, e.g. honey, propolis etc., has shown the ability to reduce reactive oxygen species (Liu et al., 2008).

Hepatoprotective activity

The hepatoprotective activity of *U. chamae* methanol root bark extract was tested *in vivo* and *in vitro*. An oral administration of the methanol extract (60 mg/kg) significantly reduced ($p < 0.05$) pentobarbitone-induced sleep in rats poisoned with acetaminophen. In this model, a protection of 92% against cytotoxicity of acetaminophen is obtained by pretreatment with the methanol extract as compared to a protection of 89.6% when the animals were pretreated with silibinin. Intraperitoneal injection of the methanol extract into rats showed no significant effect on pentobarbitone-induced hypnosis. The elevation of serum glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, alkaline phosphatase, and urea induced by paracetamol intoxication in rats was also significantly attenuated ($p < 0.05$) by the methanol extract. The methanol extract did not influence the concentration of microsomal proteins in the serum. This *in vivo* efficacy was substantiated by significant hepatoprotection on acetaminophen (AA)-induced hepatotoxicity in isolated rat hepatocytes. The methanol extract, at a dose of 1 mg/ml, remarkably ($p < 0.05$) reduced the leakage of lactate dehydrogenase in primary cultured rat hepatocytes and showed a significant effect on lipid peroxidation. The AA-induced elevation of the lipid peroxidation in rats was significantly ($p < 0.05$) decreased in the presence of *U. chamae* root bark methanol extract. A protection of 56% against the tert-butyl hydroperoxide-induced lipid peroxidation in rats was obtained by pretreatment with the methanol extract (Madubunyi, 2012). Liver-protective medicinal plants contain a variety of chemical compounds, such as phenols, coumarins, lignans, essential oils, monoterpenes, glycosides, alkaloids, carotenoids, flavonoids, organic acids and xanthines (Bhauna and Kumar, 2009) which is evident in the study above.

Antivenom activity

The venom neutralizing properties against *Naja nigricollis* venom in rats using methanol leaf extract of *U. chamae* was evaluated. To study the antivenom properties, albino rats were orally administered with a dose of 400 mg/kg body weight and 1 h later, the venom was administered intraperitoneally at a dose of 0.08 mg/kg body weight of rats. Blood clothing time, bleeding time, antipyretic activity, haemoglobin, RBC, WBC, creatine kinase, AST, ALP and ALT activities total protein antioxidant activity and some blood electrolytes, plasma urea and uric acid were measured. Results showed that *Uvaria chamae* methanol extract neutralized some biological effects of *Naja nigricollis* venom. The venom increased the rectal temperature, enzyme activities, bleeding time and other blood parameters. The plant extract was able to reduce these parameters in the extract treated groups (Omale et al., 2013). However, several chemical constituents like alkaloids, flavonoids, glucoside, and tannins have also been previously reported for anti-snake venom activity (Moreno et al., 1993; Grau and Ortiz, 1998). All these classes of chemical compounds are capable of interacting with macromolecular targets with enzymes or receptors and it can effectively inhibit the toxic effect of snake venoms *in vitro* than *in vivo* (Borges et al., 2005).

Insecticidal activity

The insecticidal effects of the powdered stem bark extract of *Uvaria chamae* and its ethanol extract was evaluated on three most devastating stored products pests (Coleopterous) in Nigeria, namely: *Callosobruchus*

maculatus F. (Bruchidae), *Rhizopertha dominica* F. (Bostrichidae) and *Sitophilus zeamais* Motschulsky (Curculionidae). It was shown that *U. chamae* powdered and ethanol stem bark extracts have potentials for use during storage of grains, ensuring food security, profit maximization and availability of seeds for the next planting season without being damaged by these test insect species which may be the responsibility of the presence of high concentration of steroids and terpenes (Negbenebor et al., 2018).

Antimalarial activity

Methanol extracts of the dried leaves and fresh fruits administered at 100 – 800 mg/kg on *Plasmodium berghei*-infected mice were evaluated using the four-day (chemosuppressive) and curative (Rane's) antimalarial test models; distilled water and amodiaquine (10 mg/kg) were negative and positive controls, respectively. At 800 mg/kg, leaf and fruit extracts gave chemosuppression of 42 and 28% (four-day test) and parasite clearance of 36.3 and 49.5% on day 5 (curative test), respectively while the positive control-treated groups were 72.8% and 98%. The leaf and fruit extracts showed better chemosuppressive and curative antimalarial activity, respectively thus justifying their folkloric uses and secondary metabolites present (Adepiti et al., 2013).

Conclusion

Uvaria chamae secondary metabolism appears to be a resource of many biologically active compounds. However, because the majority of the previous studies were focused on the biological activities of the plant extract, further investigations on the biochemical and physiological functions of active compounds and the detailed mechanisms underlying these activities are completely pivotal for the development of pharmaceutical products. More so, clinical trials concerning the rich pharmaceutical potential of *U. chamae* have been markedly neglected in previous studies. This review is hoped to be a source of enlightenment and motivation for researchers to further perform *in vitro*, *in vivo* and clinical investigations on the biological activities of *U. chamae* to gain insight into developing new potential pharmaceutical agents of commercial importance.

References

Abu T., Ajaiyeoba E.O., Abiodun O.O., Ogbole OO. 2018. Antioxidant and anti-inflammatory intestinal effect of Uvaria chamae P. Beauv (Annonaceae) in acetic acid-induced acute colitis in rats. Book of Abstract, The Nigerian society of Pharmacognosy (NSP) 30th AGM/14th scientific conference; Page 48.

Achenbach, H., Hohn, M., Waibel, R., Nkunya, M.H.H., Jonker, S.A. & Muhie, S. (1997). Oxygenated pyrenes, their potential biosynthetic precursor and benzylated dihydroflavones from two African *Uvaria* species. *Phytochemistry*; 2:395-364. http://dx:doi.org/10.1016/s0031-9422(96) 00448-7.

Adams, M.R. & Moss M.O. (1999). Food Microbiology. Cambridge: *The Royal Society of Chemistry*, pp. 471 – 476.

Adepiti A.O., Taiwo, O.E., Dada, A.D. (2013). Evaluation of the *in vivo* antimalarial potentials of the leaf and fruit of *Uvaria chamae* P. Beauv. (Annonaceae). *Planta medica*, 013.

Ake-Assi, L., Abeye, J., Guinko, S., Giguet, R. &Bangavou, Y. (1981). Contribution l'identificationet au recensement des plantes utilises dans la medicine traditionnelle et la pharmacopéeen. Republique Centrafricaine. Paris, *Agencede Cooperation Culturelle et Technique*.

Alali, F.Q., Liu, X.X. & McLaughlin, J.L. (1999).Annonaceous acetogenins: Recent progress. *J. Nat. Prod.*, 62, 504–540.http://dx:doi.org/10.1021/np980406d.

Anam, E.M., Ekpa, O.D., Gariboldi, P.V., Morah, F.N.I. & Dosunmu, M.I. (1993). 6"-Hydroxybenzyl diuvaretins and related-compounds from *Xylopia africana* (Benth) Oliver. *Indian J. Chem. B*; 32:1051–1054.

Arbonnier, M. (2000).Arbres, arbustesetlianes des zones sechesd'Afrique de l'ouest. CIRAD, MNHN, UICN. 541pp.

Arbonnier, M. (2004).Trees, Shrubs and Lianas of West African Dry Zones. Germany: *CIRAD Press Ltd.* pp. 243 - 248.Verdict Press, p. 191.

Awodiran, M.O., Adepiti, A.O. & Akinwunmi, K.F. (2017).Assessment of the cytotoxicity and genotoxicity properties of *Uvaria chamae* P. Beauv (Annonaceae) and *Morinda lucida* Benth (Rubiaceae) in mice. *Drug and chemical toxicology*, http://dx:doi.org/10.1080/01480545.2017.1365884.

Ayedoun, M.A., Moudachirou, M., Adeoti, B.S., Menut, C., Lamaty, G. & Bessiére, J.M. (1999).Aromatic plants of Tropical West Africa. VII. Essential oil of leaf and root bark of *Uvaria chamae* P. Beauv. from Benin. *Journal of Essential Oil Research* 11:23-26. http://dx:doi.org/10.1080/10412905.1999.9701060.

Basil, N. I. (2017). Antioxidant Activity of *Cnestis ferruginea* and *Uvaria chamae* Seed Extracts. *British Journal of Pharmaceutical Research*; 16(1): 1-8. http://dx:doi.org/10.9734/BJPR/2017/32924.

Bermejo, A., Figadere, B., Zafra-Polo, M.C., Barrachina, I., Estornell, E. & Cortes, D. (2005). 'Acetogenins from Annonaceae: Recent progress in isolation , synthesis and mechanisms of action'. *Natural product reports*; 22(2):269-303.http://dx:doi.org/10.1039/B500186M

Bhawna, S. &Kumar, S.U. (2009). Hepatoprotective activity of some indigenous plants.*Int. J. of Pharm. Tech. Res.*; 4:1330-1334.

Bindu. T. K. (1998). "Phytochemical investigation of a few plants" *Thesis*. Department of Chemistry, University of Calicut.

Bongers, F., Parren, M.P.E. & Traore, D. (2005). Forest Climbing Plants of West Africa: Diversity, Ecology and Management. *CAB International*. Raton, Florida, 145.

Borges, M.H., Alves, D.L.F., Raslan, D.S., Pilo-Veloso, D., Rodrigues, V.M., Homsi-Brandeburgo, M.I. & De Lima, M.E. (2005). Neutralizing properties of *Musa paradisiaca* L. (Musaceae) juice on phospholipase A2, myotoxic, hemorrhagic and lethal activities of crotalidae venoms. *J. Ethnopharmacol.*; 98:(1-2):21-29. http://dx:doi.org/10.1016/j.jep.2004.12.014

Borokini, T.I. & Omotayo, F.O. (2012). Phytochemical and ethnobotanical study of some selected medicinal plants from Nigeria. *Journal of Medicinal Plants Research;* 6(7):1106-1118. http://dx:doi.org/10.5897/JMPR09.430

Burkill, H.M. (2000). The useful plants of West Tropical Africa II. *Bot. Gardens*, Kew (k), 1: 481.

Burkill, HM. (2004).The Useful Plants of West Tropical Africa.*Royal Botanic Gardens,* Kew Pp 278-283.

Chih, H.W., Chiu, H.F., Tang, K.S., Chang, F.R. &Wu, Y.C. (2001). Bullatacin, a potent antitumor annonaceous acetogenin, inhibits proliferation of human hepatocarcinoma cell line 2.2.15 by apoptosis induction. *Life Sci.,* 69, 1321–1331.http://dx:doi.org/10.1016/S0024-3205(01)01209-7

Choi, J.S., Yokozawa, T. & Oura, H. (1991). Improvement of hyperglycaemia and hyperlipemia in streptozotocin-diabetic rats by a methanol extract of *Prunus davidiana* stems and its main component, Prunin. *Planta Medica*; 57: 208-11. http://dx:doi.org/10.1055/s-2006-960075

De Lima, A.B. (2008). Estudo da AçãoAntinociceptiva e Antiinflamatóriado 1-Nitro-2-feniletano, Pricipal Constituinte da *Anibacanelilla.M. S. Thesis, Universidade de Federal doPará, Belém*, Brazil.

Derbre´, S., Poupon, E., Gleye, C. & Hocquemiller, R.J. (2004).*Nat. Prod.*, 70: 300.

Ebi, G.C.U., Ifeanachoa, C.J. & Kamalub, T.N. (1999). Antimicrobial properties of *Uvaria chamae* stem bark. *Fitoterapia* 70: 621-624.http://dx:doi.org/10.1016/S0367-326X(99)00099-4

El-Soly, H.N., Lasswell, W.L. Jr. & Hufford, C.D. (1979). Two new c-benzylated flavanones from *Uvaria chamae* and ^{13}C NMR analysis of flavanone methyl ethers. *Journal of natural products*; 42(3):264-270.http://dx:doi.org/10.1021/np50003a003

Emordi J.E., Agbaje E.O., Oreagba I.A. & Iribhogbe I.O. (2016).Antidiabetic and hypolipidemic activities of hydroethanolic root extract of *Uvaria chamae* in streptozotocin induced diabetic albino rats. *BMC Complementary and Alternative Medicine*; 16:468. http://dx:doi.org/10.1186/s12906-016-1450-0

Ene, A.C., Egbosi, N.C., Obika, C.J., Ibegbulem, C.O., Ujowundu, C.O. &Alisi, C.S. (2016). *In vivo* Antiplasmodial Activity of Ethanol and Aqueous Extracts of *Uvaria chamae* and *Phyllantus amarus* Plants. *Futo Journal Series*; 2(2):83 – 97

Etukudo, I. (2003). Ethnobotany: Conventional and Traditional Uses of Plants. *The Verdict Press,*Uyo, Nigeria. 191p.

Fahn A (1974). Plant Anatomy. Second Edition, *Pergamon Press*, Oxford, pp. 12-550.

DOI: 10.31015/jaefs.18031

Fall, D., Gleye, C., Franck, X., Laurens, A. & Hocquemiller, R. (2002). Cis-bullatencin, a linear acetogenin from roots of *Uvaria chamae. Natuaral Product Letter;* 16(5):315-21. http://dx:doi.org/10.1080/10575630290026437

Fall, D., Duval, R.A., Gleye, C., Laurens, A. & Hocquemiller, R. (2004).Chamuvarinin, an acetogenin bearing a tetrahydropyran ring from the roots of *Uvaria chamae*. *Nat. Prod.*, 67:1041. http://dx:doi.org/10.1021/np030521a

Fall, D., Pimentel, L., Champy, P., Gleye, C., Laurens, A. &Hocquemiller, R. (2006).A new adjacent bis-tetrahydrofuran annonaceous acetogenin from the seeds of *Uvaria chamae*. *Planta medica*; 72(10):938-940. http://dx:doi.org/10.1055/s2006-941542

Grau, A. &Ortiz, A. (1998). Dissimilar protection of tocopherol isomers against membrane hydrolysis by phospholipase A_2.*Chem Phys Lipids*; 91(2):109-118. http://dx:doi.org/10.1016/S0009-3084 (97)00101-1

Hassig, A., Liang, W.X., Schwab, H. &Stampfli, K. (1999). Flavonoids and tannins: Plant-based antioxidants with vitamin character. *Med Hypotheses*; 52: 479–81. http://dx:doi.org/10.1054/mehy.1997.0686

Hertog, M.G.L., Feskens, E.J.M, Hollman, D.C.H., Katan, M.B. & Kromhout, D. (1993). Dietary antioxidant flavonoids and risk of coronary heart disease.The Zutphen Elderly study. *Lancet*, 342: 1077-1011. http://dx:doi.org/10.1016/0140-6736(93)92876-U

Hufford C.D. & Lasswell W.J Jr. (1976).Uvaretin and Isouvaretin. Two novel cytotoxic c-benzyl flavanone from *Uvaria chamae*. *J. Org. Chem.,* 41(7):1297-1298. http://dx:doi.org/10.1021/j000869a062

Hufford, C.D. & Oguntimein, B.O. (1980). Dihydrochalcones from *Uvaria angolensis*. *Phytochem*; 19(9):2036-2038. http://dx:doi.org/10.1016/S0031-9422(80) 83036-6

Hufford, C.D. & Lasswell, W.L., (1978). Anti-microbial activities of constituents of *Uvaria chamae*.*Lloydia* , 41,156–160.

Igoli, J.O., Ogaji, O.G., Tor-Anyiin, T.A. & Igoli, N.P. (2005). Traditional Medicine Practice amongst the Igede People of Nigeria. Part II. *Afr. J. Trad*. CAM. 2(2): 134 – 152.

Iwu, M.M. (1993). *Handbook of African Medicinal Plants*.CRC Press, Boca.22.495**.**

Katerere, D.R., Gray, A.I., Nash, R.J. &Waigh, R.D. (2012). Phytochemical and antimicrobial investigations of stilbenoids and flavonoids isolated from three species of Combretaceae. *Fitoterapia*, 83(5):932-940. http://dx:doi.org/10.1016/j.fitote.2012.04.011

Kone, M., Toure, A., Ouattara, K. &Coulibaly, A. (2015). Phytochemical Composition, Antioxidant and Antibacterial Activities of Root of *Uvaria chamae*P. Beauv. (Annonaceae) Used in Treatment of Dysentery in North of Côte d'Ivoire. *International Journal of Pharmacognosy and Phytochemical Research*; 7(6); 1047-1053.

Lasswell, W.J Jr. & Hufford C.D. (1977). Cytotoxic c-benzylatedflavanoids from *Uvaria chamae*. *Phytochem.*, 16:1441. http://dx:doi.org/10.1021/jO00428a006

Liu, R., Gao, M., Yang, ZH. & Du, GH. (2008). Pinocembrin protects rat brain against oxidation and apoptosis induced by ischemia-reperfusion both *in vivo* and *in vitro*. *Brain Res.*, 1216:104-115. http://dx:doi.org/10.1016/j.brainres.2008.03.049

Liu, X., Kim, J., Li, Y., Li, J., Liu, F. & Chen, X. (2005). Tannic acid stimulates glucose transport and inhibits adipocyte differentiation in 3T3-Li cells. *J Nutr*.; 135: 165-71.

Mabberly, D.J. (1997). *The Plant – Book*, 2nd Ed. Cambridge University Press, UK, 41-42.

McLaughlin, J.L. (2008). Paw Paw and Cancer: Annonaceous Acetogenins from Discovery to Commercial products. *Journal of Natural products*; 71(7):1311-1321. http://dx:doi.org/10.1021/np800191t

Madubunyi, I.I., Njoku, C.J., Ibeh, E.O. &Dume A.B. (1996).Antihepatotoxic and trypanocidal effects of the root bark extract of *Uvaria chamae*. *International Journal of pharmacognosy*; 34(1):34-40.

Madubunyi, II. (2012). Hepatoprotective activity of *Uvariachamae* root bark methanol extract against acetaminophen-induced liver lesions in rats. *Comparative Clinical Pathology*; 21(2):127-135.http://dx:doi.org/10.1007/S00580-010-1072-8

Manikandan, L., Senthilkumar, GP., Rajesh, L.T. & Suresh, R. (2006). Cancer chemoprotective agents from medicinal plants. In: Trivedi PC (ed). *Medicinal Plants: Ethnobotanical approach.* Agrobios., India. P. 410.

Mariita, P.M., Ogol, C.K.P.O., Oguge, N.O. & Okemo, P.O. (2011). Methanol extract of three medicinal plants from samburu in Northern Kenya show significant antimycobacterial, antibacterial and antifungal properties. *Res. J. of Med. Plant*, 5:54-64. http://ir-library.ku.ac.ke/handle/123456789/5932

Marshall, S.J., Russel, P.F., Phillipson J.D., Kirby, G.C., Warhurst, D.C. &Wight, C.W. (2000). Antiplasmodial and antiamoebic activities of medicinal plants from Sieria Leone. *Phytotherapy Research*; 14(5):356-358. http://dx:doi.org/10.1002/1099-1573(200008)14:5<356::AID-PTR636>3.0.CO;2-Z

Meiselman, H.L., Halpern, B.P. & Dateo, G.P. (1976). Reduction of sweetness judgments by extracts from the leaves of *Ziziphus jujuba*. *Physiol Behavior*; 17: 313-17. http://dx:doi.org/10.1016/0031-9384(76)90081-0

Metzner, J. & Schneidewind, E.M. (1978). Effect of pinocembrin on the course of experimental *Candida* infections in mice. *Mykosen*, 21(8):257-262.

Moreno, J.J. (1993). Effect of aristolochic acid on arachidonic acid cascade and in vivo models of inflammation. *Immunopharmacology*; 26(1):1-9. http://dx:doi.org/10.1016/0162-3109(93)90061-T

Moses, S.O., Olowu, R., Adewale, N.S.D. &William, N.S. (2013). 1-Nitro-2-phenylethane dominates the chemical composition of the leaf essential oil of *Uvaria chamae* from Badagry, Nigeria. *American Journal of Essential Oils and Natural Products*; 1 (1): 48-50.

Moukimou,A.O., dc Pascal, A., Annick, B., Yaya, K., Pierre, N.A., Felicien, A. &Dominique S.K. (2014). Chemical characterization and biological activities of extracts of three plants used in traditional medicine in Benin: *Tectona grandis, Uvaria chameae* and *Justicia secunda*. *Asian J Pharm Clin Res*, 7(5): 23-27.

Negbenebor, H. E., Makanjuola, W. A., Denloye, A. A. and Nura, S. (2018). Toxicity of powdered and ethanolic extracts of *Uvaria chamae* (Annonaceae) Bark on selected stored product insect pests. *African Journal of Biotechnology*, Vol. 17(11), pp. 350-355. http://dx:doi.org/10.5897/AJB2017.16257

Nkunya, M.H.H., Weenen, H., Reener, C., Waibel, R. & Achenbach, H. (1993). Benzylated dihydrochalcones from *Uvaria leptocladon*. *Phytochemistry*; 32(5):1297-1300. http://dx:doi.org/10.1016/S0031-9422(00)95109-4

Nwosu, M. (2000). Plant resources used by women as herbal medicines and cosmetics in Southeastern Nigeria. *Arztezeitschrift for naturopathy,* 41(11):760-7.

Oguntimein, B., Ekundayo, O., Laakso, I. & Hiltunen, I. (1989). Volatile constituents of *Uvaria chamae* leaves and root bark. *Planta Medica* 55:312-313. http://dx:doi.org/10.1055/S-2006-962016

Okorie, D.A. (1977). New benzyldihydrochalcones from *Uvaria chamae. Phytochem.*; 16(10):1591-1594. http://dx:doi.org/10.1016/0031-9422(77) 84030-2

Okwu, D.E, & Iroabuchi, F. (2009). Phytochemical Composition and Biological Activities of *Uvaria chamae* and *Clerodendoron splendens*.*E-J Chem*.; 6:553–60.

Oluremi, B.B. & Adeniji, J.A. (2015).Anti-viral Activity Evaluation of Selected Medicinal Plants of Nigeria against Measles Virus. *British Microbiology Research Journal*; 7(5): 218-225. http://dx:doi.org/10.9734/BMRJ/2015/16220

Oluremi, B.B., Osungunna, M.O. & Omafuma O.O. (2010). Comparative assessment of antibacterial activity of *Uvaria chamae* parts. *Afr. J. Microbiol. Res*. 4 (13):1391-1394.

Omale, J., Ebiloma U.G. & Idoko G.O. (2013). *Uvaria chamae* (Annonaceae) plant extract neutralizes some biological effects of *Naja nigricollis* snake venom in rats. *Br. J. Pharmacol. Toxicol*., 4(2):41-50.

Park, R. J. & Sutherland, M. D. (1969). Some constituents of *Apium leptophyllum* (d.C.) F. Muell. in relation to tainting of milk. *Australian J. Chem.*, 22(3):495-6.

Peana, A.T., D'Aquila, P.S., Chessa, M.L., Moretti, M.D.L., Serra, G. &Pippia, P. (2003). (–)-Linalool produces antinociception in two experimental models of pain. *Eur. J. Pharmacol*., 460:37-41.http://dx:doi.org/10.1078/094471102321621322

Peana, A.T., D'Aquila, P.S., Panin, F., Serra, G., Pippia, P. & Moretti, M.D.L. (2002). Anti-inflammatory activity of linalool and linalyl acetate constituents of essential oils. *Phytomedicine*; 9:721-726.

Philipov, S., Ivanovska, N., Istatkova, R., Velikova, M. & Tuleva, P. (2000). Phytochemical study and cytotoxic activity of alkaloids from *Uvaria chamae* P. Beauv. *Die Pharmazie*; 55:688-689.

Ruddock, P.S., Charland, M., Ramirez, S., Lopez, A., Neil Towers, G.H., Arnason, J.T., Liao, M. & Dillon, J.A. (2011). Antimicrobial activity of flavonoids from *piper lanceaefolium* and other Colombian medicinal plants against antibiotic susceptible and resistant strains of *Neisseria gonorrhoeae*. *Sex Transm Dis*.38(2):82-88. http://dx:doi.org/10.1097/OLQ.Ob013e3181fobdbd

Sala, A., Recio, M.C., Schinella, G.R., Manez, S., Giner, R.M., Cerda-Nicolas, M. &Rosi, J.L. (2003). Assessment of the anti-inflammatory activity and free radical scavenger activity of tiliroside. *Eur. J. Pharmacol*., 461(1):53-61. http://dx:doi.org/10.1016/S0014-2999(02)02953-9

Salisbury, F.B, & Ross, C.W. (1992).'Mineral nutrition'. *Plant Physiology*. Wadsworth pp. 357-407, pp. 531-548.

Sofowora, E.A (1982). *The State of Medicinal Plants' Research in Nigeria*. Ibadan University Press, Nigeria, p. 404.

Soromou, L.W., Chu, X., Jiang, L., Wei, M., Huo, M., Chen, N., Guan, S., Yang, X., Chen, C., Feng, H. & Deng, X. (2012). *In vitro* and *in vivo* protection provided by pinocembrin against lipopolysaccharide-induced inflammatory responses. *Int. immunopharmacol*., 14(1):66-74. http://dx:doi.org/10.3109/1547691X.2013.7

Suba, V., Murugesan, T., Rao, B.R., Ghosh, L., Pal, M., Mandal, S.C. & Saha, B.P. (2004). Antidiabetic potential of *Barleria lupulina* extract in rats. *Fitoterapia*, 75: 1-4. http://dx:doi.org/10.1078/0944-7113-00316

Tempesta, M.S., Kriek, G.R. &Bates, R.B. (1982). Uvaricin, a new antitumor agent from *Uvaria accuminata* (annonaceae). *J. Org. Chem.*, 47, 3151–3153. http://dx:doi.org/10.1021/j000137a024

Thierry, C.A., Joachim, D.G., Salomé Kpoviessi, D.S., Georges, C.A, Moudachirou, M. & Gbeassor, M. (2012). Antihemolytic Properties of Extracts of Six Plants Used in the Traditional Treatment of Sickle Cell Disease in Benin. *Journal of Applied Pharmaceutical Science*, 02 (03): 08-13.

Trease, G.E & Evans, W.C. (1989). *Textbook of Pharmacognosy*.14th Edition.W.B. Sanders, London.

Uzel, A., Sorkun, K., Oncag, O., Cogulu, D., Gencay, O. & Salih, B. (2005). Chemical compositions and antimicrobial activities of four different Anatolian propolis samples. *Microbiol. Res*., 160(2):189-195. http://dx:doi.org/10.1016/j.micres.2005.01.002

Zafra-Polo, M.C., Figadère, B., Gallardo, T., Tormo, J. & Cortes, D. (1998). Natural acetogenins from annonaceae, synthesis and mechanisms of action. *Phytochemistry;* 48(7):1087–1117. http://dx:doi.org/10.1016/S0031-9422(97)00917-5

Zafra-Polo, M.C., González, M.C., Estornell, E., Sahpaz, S. & Cortes, D. (1996). Acetogenins from annonaceae, inhibitors of mitochondrial complex I. *Phytochemistry*, 42, 253–271. http://dx:doi.org/10.1016/0031-9422(95)00836-5