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REVIEW ARTICLE

Research progress in phytochemistry and biology of *Aframomum* species

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ABSTRACT

Context: The African genus *Aframomum* (Zingiberaceae) is a group of diverse tropical plants frequently collected yet largely neglected taxonomically. The current and unprecedented loss of species due to man-made habitat destruction and climate change adds a desperate urgency not only to understand the phylogenetics, chemotaxonomy and biology, but also to preserve the quickly disappearing species.

Objectives: The present systematic review reports on the research progress in phytochemistry, pharmacology and toxicology of *Aframomum* species.

Methodology: Scientific databases such as MedSci, PubMed, Scopus, Google Scholar and Web of Knowledge were used to retrieve publications (from the year 1990 to 2014) related to *Aframomum* plants, isolated compounds and their bioactivity, phytochemistry and toxicology. The keywords combinations for the search were: *Aframomum*; chemotaxonomy, phylogenetics, pharmacology and bioactive metabolites and toxicology. A total of 71 research articles that report on the biological activity of extracts and chemical constituents were recovered and presented in this review.

Results: Most published data related to the potential of *Aframomum melegueta*, a medicinal plant from West and Central Africa. The potential of phenols and terpenoids isolated from *Aframomum* plants were generally much better documented than that of arylalkanoids.

Conclusion: *Aframomum* genus represents an enormous resource for novel compounds with a range of medicinal properties. However, these plants are under-researched and their conservation is poor. To unravel their full potential, efforts should be strengthened throughout the continent to establish the taxonomy, preserve the genus and explore novel medicinal properties.

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Introduction

The Zingiberaceae constitute a family of terrestrial rhizomal herbs with over 1400 species distributed in over 50 genera. The genus *Aframomum* Schumann (1904) is the largest genus of Zingiberaceae comprising of 80 species of giant herbs peculiar to West and Central Africa. The genus was described by K. Schumann (1904) to accommodate the African species of *Amomum* (Cheek et al. 1996). *Aframomum* species range from Senegal in the west to Ethiopia in the north and Angola to Madagascar in the south. It is also found in the Gulf of Guinea Islands, Sao Tome and Principe. Some species, however, are ecologically specialized; for example, *Aframomum longiligulatum* is known only from forests in Cameroon, while the flooded forest in the Congo River basin is dominated by *Aframomum pseudostipulare*. *Aframomum alboviolaceum* is only found in the Savanna (Larsen et al. 1998; Tane et al. 2005). *Aframomum* species are also found in light gaps and forest margins and are common along roads and in old fields. They are perennials and aromatics when any part of the plant is crushed. They also possess highly coloured flowers and the peduncles are covered with sterile overlapping bracts (Fankam et al. 2011). These varieties of species are mostly used as laxatives, anthelmintics, toothache, anti-diarrhoea, fever management, stomach ache, inflammatory conditions, post-partum haemorrhage and a tonic for sexual stimulation (Duke 2002). Additionally, they are reported to have anti-ulcer, anti-microbial, antinociceptive, antiplasmodial, hepatoprotective and anticancer activities (El-Halawany et al. 2014).

Various compounds have been isolated from the *Aframomum* plants since the 1970s and their chemistry and pharmacology

have been reported (Adegoke & Skura 1994; Escoubas et al. 1995). Plant selection based on prior ethnomedicinal use has been fairly predictive of the possibility of identifying active leads (Kueté 2010). For example, ethnopharmacological uses as immune and skin disorders, and inflammatory ailments, should be considered when selecting plants to treat cancer symptoms (Kueté & Efferth 2010). The classes of compounds generally found in *Aframomum* species include diterpenoids, sesquiterpenoids, arylalkanoids and flavonoids. In this brief review, we summarize the recent progress in phytochemical and biological research of some of the most exploited *Aframomum* plants. Studies on the chemotaxonomy and molecular phylogeny are still under investigation to facilitate further conservation and exploitation of *Aframomum* pharmaceutical and food resources.

Molecular taxonomy, phylogeny and genomics

The taxonomy of *Aframomum* is extremely difficult and the genus is currently undergoing revision (Lock & Hall 1975). According to Harris et al. (2000), *Aframomum* is monophyletic and is thought to have diversified during the late Oligocene to the Miocene. Presently, no criteria for the recognition of these species at the generic level has been established but studies using molecular sequence data (*ITS-nrDNA* and *trnl-f-cpDNA*, *matK*) have been utilized to generate hypotheses on the phylogenetic relationships among the genera of the Zingiberaceae, to evaluate past classifications of the family and to identify morphological features that characterize the various clades (Babu et al. 2011, 2012). The chloroplast region, *psbA-trnH* intergenic spacer has been proposed

as a useful marker for DNA barcoding (Shaw et al. 2007). However, the sequencing has been reported to be hard, time-consuming and many of the *psbA-trnH* sequences are of poor quality. It was later observed that adding internally transcribed spacer region (ITS) and *trnL-F* databases improved the resolution of the phylogenetic tree. Hence, it is concluded that *PsbA-trnH* intergenic spacer alone might not be the most suitable for distinguishing taxa at the species level. Based on the DNA sequences of ITS, a system of classification was proposed. The genera of Zingiberaceae were grouped as: *Alpinia*, *Aframomum*, *Amomum* and *Elettariopsis* (which is near to *Elettaria*), *Renealmia*, *Plagiostachys*, *Vanoverberghia*, *Hornstedtia* and *Etingera* in a single clade 'Alpineae', whereas *Hedychium*, *Zingiber* and *Curcuma* formed another clade 'Zingibereae' (Kress, Liu, et al. 2005; Kress, Wurdack, et al. 2005). This significant discrepancy in the chloroplast phylogenies might be due to intraspecific polymorphism and introgression. More studies are needed at population or species level to ensure a better characterization of *Aframomum* species.

Chemotaxonomy of Aframomum

Chemotaxonomy or chemosystematics is the attempt to classify and identify organisms (originally plants), according to demonstrable differences and similarities in their biochemical compositions (Smith 1976). Generally, it has been observed that plants of the same family usually synthesize compounds of similar classes due to the presence of similar classes of enzymes and hence similar biosynthetic pathways (Kuetze & Efferth 2010). The *Aframomum* species as well as other Zingiberaceae are best known for the production of labdane diterpenoids and flavonoids. Other classes of compounds encountered in the genus include sesquiterpenoids and arylalkanooids. Out of the 12 most chemically studied *Aframomum* species, at least 11 contain diterpenoids (Tane et al. 2005). Within the Zingiberaceae family, labdane diterpenes and flavonoids may represent a chemotaxonomic marker of the genus *Aframomum*. However, *Aframomum arundinaceum* is one of the few species of *Aframomum* from which sesquiterpenoids are reported (Ayimele et al. 2004; Wabo et al. 2006).

Pharmacology of Aframomum extracts

Antioxidant and anti-inflammatory activity

The enzymatic sources of ROS/RNS include NADPH oxidase, xanthine oxidase, uncoupled endothelial nitric oxide synthase, arachidonic acid metabolizing enzymes such as cytochrome P450 enzymes, lipoxygenase (LOX) and cyclooxygenase (COX), and the mitochondrial respiratory chain. In a recent research conducted by El-Halawany et al. (2014), it was found that methanol-chloroform extracts of *A. melegueta* significantly exhibited a protective role in CCl₄-induced acute liver injury which might be due to elevated antioxidative defence potentials, suppressed inflammatory responses and apoptosis of liver tissue. Ethanolic extract of *A. melegueta* seeds also possessed anti-inflammatory activity, which was in part due to the inhibition of COX-2 enzyme activity and expression of pro-inflammatory genes (Ilic et al. 2014). Scavenging of free radicals is one of the major antioxidative mechanisms to inhibit the chain reaction of lipid peroxidation (LPO) and reduction of the deleterious effect of the cytotoxic products. Administration of aqueous extract of *A. melegueta* seeds to gamma radiation-induced liver damaged male Wistar rats at a dose of 200 or 400 mg/kg before and after irradiation was reported to have significantly decreased the elevated levels of

LPO, restored glutathione (GSH) level near normal and enhanced catalase and glutathione peroxidase activities as well as significantly decreased the elevated levels of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities (Nwozo & Oyinloye 2011).

Inflammation is an important component of immune response to pathogens and damaged cell characterized by heat, redness, pains, swelling and sometimes loss of tissue functionality in chronic situation (Zhang & McNaughton 2006). The body's reaction to this phenomenon may trigger inflammatory responses through the release of pro-inflammatory eicosanoids such as prostaglandins, prostacyclins and leukotrienes, and pro-inflammatory cytokines such as interleukins (IL-1B, IL-3, IL-6), interferons, tumour nuclear factor (TNF- α) and platelet-activating factor. COX and LOX oxidation of polyunsaturated fatty acid such arachidonic acid or linoleic acid forming bioactive eicosanoids are the major features of inflammatory response (Haeggström et al. 2010).

Phenolics, alkaloids and triterpenoids have been demonstrated to exhibit anti-inflammatory activities by exerting antioxidative properties in reducing O²⁻ and malondialdehyde (MDA) production, plasma extravasations and cell migration mainly of leukocytes and potentiates the activity of superoxide dismutase in radical scavenging (Mosquera et al. 2007). Ethanolic extract of *A. melegueta* seeds demonstrated an anti-inflammatory activity in a rat paw oedema model and in pro-inflammatory gene expression assays. The whole extract reduced inflammation by 49% at 1000 mg/kg. The activity was in part attributed to the inhibition of COX-2 enzyme and expression of pro-inflammatory genes by [6]-paradol (23) and [6]-Shogaol (25) (Ilic et al. 2014).

Anticancer activity

Cancer cells rapidly acquire multidrug resistance (MDR), mainly due to the presence of two adenosine triphosphate-binding cassette transporters. MDR cancer cells reveal cross-resistance to a variety of chemically and functionally unrelated drugs. The structural diversity of plant's secondary metabolites makes them an indispensable source for the discovery of new cytotoxic agents. Methanolic extracts of *A. arundinaceum* seeds demonstrated moderate, but selective, cytotoxicity towards leukaemia CEM/ADR5000 cells and glioblastoma U87MG Δ EGFR compared to their respective sensitive counterparts CEM/CEM and U87MG cell lines (Kuetze et al. 2014). One study noted that *A. melegueta* methanolic and chloroform seed extracts held cytotoxic potential against PANC-1 pancreatic cancer cells *in vitro* with IC₅₀ values of 13.8 μ g/mL and 47.8 μ g/mL, respectively (Obike et al. 2014).

Antimicrobial activity

Many of the plant extracts and fractions used have good activities, especially the non-polar fractions of hexane and dichloromethane against the pathogens tested, and this may explain the traditional use of these medicinal plants. Plants of the genus *Aframomum* are known for their antibacterial activities, and this has been assigned to the presence of terpenoids such as aframodial (Ayafor et al. 1994a). Recently, great attention is being paid to exploitation of *Aframomum* plants as biodegradable fungicides in the control of most plant pathogenic fungi. Non-polar hexane seed extract of *Aframomum sceptrum* has been found to show the highest percentage inhibition of 60.26% against *Hypocrea lixii* (IMI 501885) while the polar ethanolic extracts with a percentage inhibition of 52.73% against *Fusarium f. sp. elaeidis*. Non-polar acetone seed

extract and methanol extract showed the lowest percentage inhibitions of 42.45% against *Fusarium oxysporum* f. sp. *elaedis* and 42.31% against *H. lixii*, respectively (Okogbenin et al. 2014). *Aframomum melegueta* has been reported to inhibit *Bacillus cereus* (a pathogen obtained from vegetable salad) with a lowest minimum inhibitory concentration of 31.25 mg/mL. This spice has henceforth been recommended to help in ensuring food safety (Uzeh & Oguntosin 2013). The difference in antimicrobial properties of a plant extract might be attributable to the age of the plant used, freshness of plant materials, physical factors (temperature, light and water), contamination by field microbes, adulteration and substitution of plants, incorrect preparation and dosage (Okigbo & Igwe 2007). It has also been reported that inactivity of plant extracts may be due to the age of the plant, extraction solvent, method of extraction and time of harvest of the plant materials (Alo et al. 2012).

Antidiabetic and antiobesity activity

Aqueous leaf extract of *A. melegueta* showed hypoglycemic activity on alloxan-induced diabetic and non-diabetic rats. The antihyperglycemic activity of the aqueous leaf extract was associated with an increase in plasma insulin level suggesting an insulinogenic activity, stimulating insulin secretion from the remnant β -cells or from regenerated β -cells (Adefegha & Oboh 2012b). Ethanolic extract of *A. melegueta* seeds [10 mg of 15.2% 6-gingerol (24), 12.5% 6-paradol (23), 1.7% 6-shogaol (25) and 4.0% 6-gingeredione] was able to increase the metabolic rate by increasing the energy expenditure through the activation of brown adipose tissue, a site of sympathetically mediated metabolic thermogenesis. Persons with no response to cold exposure (without substantial brown fat adipose tissue) failed to show a response (Sugita et al. 2013).

Antihypertensive activity

Lawal et al. (2007) reported that, ingestion of *A. melegueta* seeds resulted in the lowering of cardiovascular indices such as systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure and mean arterial pressure in normotensives and hypertensives, respectively. All were found to be significantly different from control values ($p < 0.01$). Percentage reductions, though similar between normotensives and hypertensives, were however greater for SBP averaging (15–16%) than DBP (9–10%). A central effect was suggested as the cause but peripheral vasodilatation effect was not equally ruled out probably via the nitric oxide-cGMP pathway. The degree of reduction was found to be within safety limits, indicating its potential usefulness in managing hypertension in young and elderly hypertensive patients.

Male sex organs

The administration of 115 mg/kg of aqueous seeds extract of *A. melegueta* daily for 8 days resulted in an increase in the penile erection index, frequency of genital grooming and genital sniffing, and an increase in mounting frequency by 54%. Intromission latency was reduced by 32%, while ejaculation latency was increased (delayed) by 60% (with no significant influence on post-ejaculatory interval), and while all these effects were greater than control they were simultaneously lesser than the other herb tested, *Piper guineense* (although not by a statistically greater degree) (Kamtchouing et al. 2002). The same was also observed to

increase the secretions of epididymis and seminal vesicle, which are accessory sex organs (Mbongue et al. 2012).

Anti-estrogenic activity

El-Halawany and Hattori (2012) reported that methanolic seeds extracts of *A. melegueta* inhibit $56.7 \pm 3.4\%$ of estrogenic activity in a yeast assay at the concentration of 100 $\mu\text{g/mL}$; this was decreased with naringinase pretreatment. Despite *A. melegueta* outperforming all other herbs in this study, it underperformed relative to the active control of tamoxifen (78% inhibition at 10 μM).

Anti-ageing activity

An assay based on image processing analysis demonstrated the antiwrinkle activity of a formulation containing *Aframomum angustifolium* seed extract. The data obtained in the two centre study suggests that the cosmeceutical containing *A. angustifolium* seed extract produces a global rejuvenation effect in terms of redness, pigmentation and fine lines similar to that noted utilizing an intense pulse light source. More research is currently under investigation (Andre et al. 2008)

Spasmolytic activity

The spasmolytic properties of the aqueous seed extracts of *A. melegueta* and *Citrus aurantifolia* (Christm and Panzer) (AMCA) mixture were tested on isolated rat trachea. Inhibition of the contraction was observed in the presence of the AMCA (EC_{50} 1.80 \pm 0.48 mg/mL) after a precontraction of the trachea by acetylcholine (10^{-5} M). The extract did not involve muscarinic receptor but likely inhibited cellular calcium. It also involved in part, β -adrenergic receptors (Ahounou et al. 2012).

Chemical components of the genus *Aframomum* and their biological activities

Terpenoids: diterpenoids and sesquiterpenoids saponins

Diterpenoids (C_{20}) and sesquiterpenoids (C_{15}) are secondary metabolites of terpenoids. Their general chemical structures contain isoprene ($\text{C}_{10}\text{H}_{16}$). In medicinal plants, these compounds are also called quinta essentia, or essential oil fraction. Other terpenes include triterpenes, tetraterpenes and hemiterpenes (C_{30} , C_{40} and C_5). Some diterpenoids, aulacocarpinolide (2), aulacocarpin A (3) and aulacocarpin B (4) have been isolated from *Aframomum aulacocarpos*. Sesquiterpenoids are rarely found in *Aframomum* species. Up to date only three sesquiterpenoids derivatives have been reported in these species, these are 6,7-epoxy-3(15)-caryophyllene (20) and (-)- α -bisabolol (21) found in *A. arundinaceum*, (+)-S-nerolidol (19) isolated from *A. sceptrum* and *Aframomum escapum* (Ayafor et al. 1994b; Tomla et al. 2002; Wabo et al. 2006).

Antiplasmodial and antimicrobial activity

Diterpenoids and sesquiterpenoids are active against bacteria, fungi, viruses and protozoa. Some of the active metabolites that have been isolated are: labdane 3-deoxyaulacocarpin A from *Aframomum zambesiaceum*; sesquiterpenoids oplodiol, (5E,10(14)-germacradien-1 β ,4 β -diol and 1(10)E,5E-germacradien-4 α -ol) with

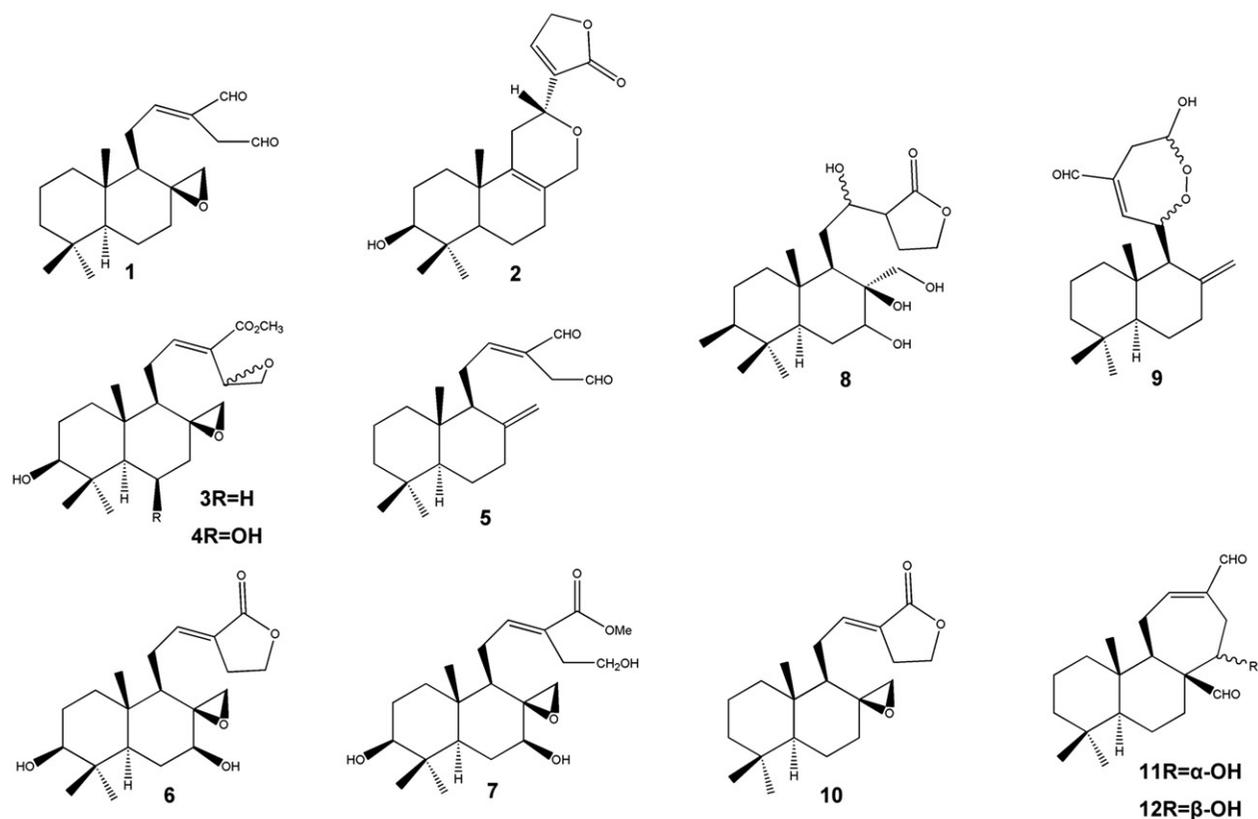


Figure 1. Structures of terpenoids (1–12).

respective IC_{50} values of 4.17, 1.63 and 1.54 μM (Tchuendem et al. 1999; Kenmogne et al. 2006). In all cases, antiplasmodial activity was measured by inhibition of the chloroquine resistant W2 *P. falciparum* strain with $IC_{50} < 5 \mu\text{M}$. The mechanism of action of terpenes is not fully understood, but is speculated to involve membrane disruption by the lipophilic compounds. Also, terpenoid molecules could insert into cell membrane and modify the composition, influence membrane fluidity, and potentially affect signalling by ligands and cofactors (Hao et al. 2013). Aframodial (dialdehyde, 8 β ,17-epoxy-12E labdane-15,16-dial) (1) has been isolated from the seeds of *Aframomum polyanthum*, *Aframomum masuiianum*, *Aframomum kayserianum*, *Aframomum sulcatum*, *Aframomum longifolius*, *A. arundinaceum* and *Aframomum latifolium* (Ayafor et al. 1994a). Aframodial has been reported to actively inhibit growth of *Salmonella enteritidis*, *Pseudomonas fragi*, *P. fluorescens*, *Proteus vulgaris*, *Staphylococcus aureus*, *Aspergillus flavus*, *Streptococcus pyogenes*, *A. parasiticus*, *A. ochraceus* and *A. niger* in the bioassays of the extracts of *Aframomum danielli*. Their zones of inhibition in mm were 20, 22.33, 22.27, 23.29, 28.09, 26.54, 23.90, 33.95, 32.0 and 28.78, respectively (Adegoke & Skura 1994). It has also been reported that the extract of *A. polyanthum* is active against *Enterobacter aerogenes* EA294 with the lowest recorded minimal inhibitory concentration of 32 $\mu\text{g/mL}$ (Djeussi et al. 2013). Other plant extracts that have also been found to possess antimicrobial activity include *Aframomum giganteum* (Agnaniet et al. 2004), and *A. danielli* (Fasoyiro & Adegoke 2007).

Anticancer activity

Recent studies on the cytotoxicity of four *Aframomum* species (*A. arundinaceum*, *A. albviolaceum*, *A. kayserianum* and *A. polyanthum*) towards multi-factorial drug resistant cancer cell lines

reported cytotoxic potential of *Aframomum* species and highlights the good activity of *A. arundinaceum* on sensitive and drug-resistant cancer cell lines. This must have been contributed by galanals A (11) and B (12), naringenin and kaempferol-3,7,4'-trimethyl ether (30). However, galanal A (11) and galanal B (12) were generally less active towards resistant cancer cells, with galanal B showing collateral sensitivity towards resistant breast adenocarcinoma MDA-MB-231/BCRP cells (Kuate et al. 2014). *A. melegueta* is reported to have inhibited the proliferation of the leukaemia ADR5000 cell lines with a reported IC_{50} value of 7.80 $\mu\text{g/mL}$ (Kuate et al. 2011). Naringenin has also shown cytotoxicity in various human cancer cell lines and induced apoptosis via a transient induction of caspase-3/CPP32 activity, in the human promyeloleukaemia cell line HL-60 (Kanno et al. 2003; Li et al. 2009). The moderate cytotoxicity of galanals A (11) (IC_{50} of 18 μM or 5.62 $\mu\text{g/mL}$) and B (12) (IC_{50} of 32 μM or 12.21 $\mu\text{g/mL}$) towards human T lymphoma Jurkat cells has also been reported (Miyoshi et al. 2003) (Figures 1 and 2)

Polyphenols, flavonoids and phenolic glycosides

The relationship between total phenol contents and antioxidant activity has been widely studied in different foodstuffs (Ghasemi et al. 2009). Antioxidant activity of foodstuff significantly increases with the presence of high concentration of total phenol and flavonoid contents. Phenols are broadly distributed in plants and are the most abundant secondary metabolites. Plant phenols have drawn increasing attention due to their significant effects in the prevention of multiple oxidative stress associated diseases such as cancer. Flavonoids (hydroxylated phenolic substances) have shown great potential in management of coronary heart disease (Rice-Evans et al. 1997) and effective against a wide array of microorganisms such as polio type 1 and Coxsackie B4 viruses

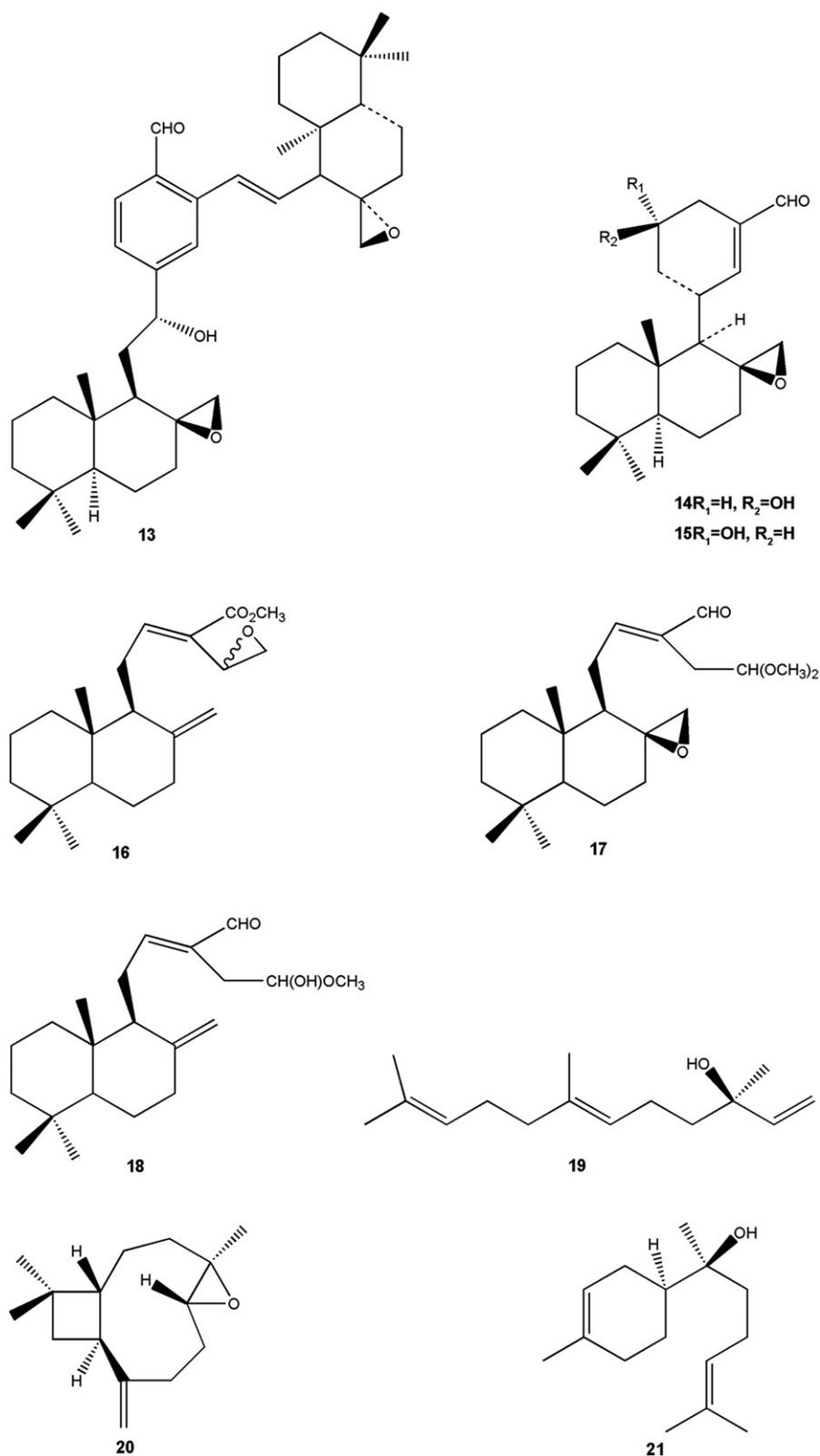


Figure 2. Structures of terpenoids (13–21).

(Özçelik et al. 2011). Flavonoids are also known to act on the inflammatory response via many routes and block molecules like COX, iNOS, cytokines, nuclear factor- κ B and matrix metalloproteinases.

Amarowicz and Shahidi (1997) attributed the pharmacological activities (antiulcer, anti-inflammatory, antiallergic, antiviral, antibacterial, antiosteoporotic, and antihepatotoxic actions) of

flavonoids to their potent antioxidant activities. In addition, flavonoids are good free radical scavengers that donate hydrogen, inhibit LPO and are metal ion chelators. However, the antioxidant power of flavonoids depends on some important structural prerequisites such as the number and the arrangement of hydroxyl groups, the extent of structural conjugation and the presence of electron-donating and electron-accepting substituents on the ring

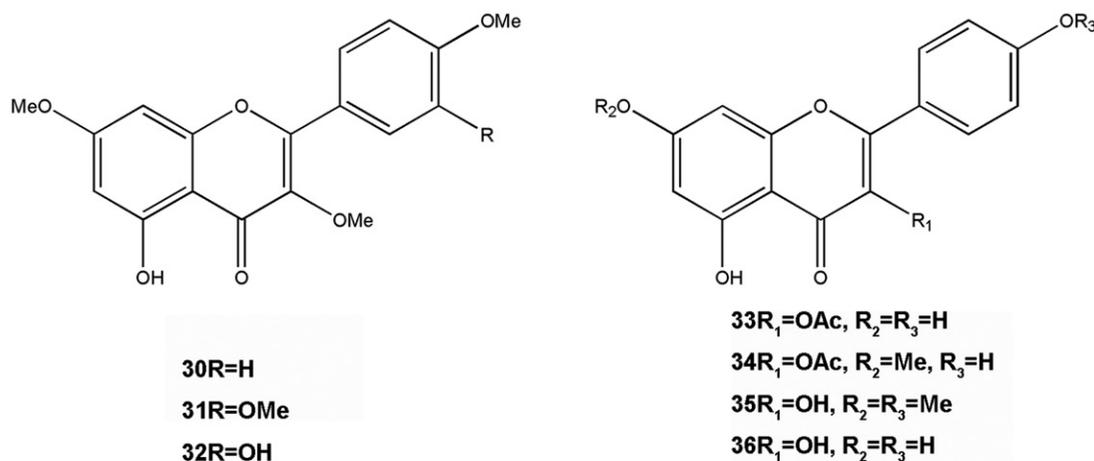


Figure 3. Structures of flavonoids.

structure (Middleton et al. 2000). Eight flavonoids reported in five different species of the genus are summarized in Figure 3.

Antioxidant activity

In general, ortho-substitution with an electron donor, such as the methoxy groups of curcumin, increases the antioxidant activity of phenols by enhancing the stability of the phenoxyl radical by an inductive effect (El-Halawany et al. 2014). RP-HPLC analysis showed abundance of quercetin and kaempferol in phenolic characterization on seeds of *A. melegueta* and chlorogenic acid in *A. danielli*. These phenolic and non-phenolic constituents contributed to the inhibitory effect of these extracts on acetylcholinesterase activity and their antioxidant property (Adefegha & Oboh 2012a). Among all the *Aframomum* species, *A. melegueta* has captured attention to possess functional ingredients to prevent inflammation and ROS-related diseases. Quercetin and kaempferol isolated from *A. giganteum* has been shown to possess antibacterial activities. They also display potent antiviral and anti-inflammatory activities. In addition, quercetin and kaempferol inhibit the release of rat mast cell histamine, and they are also efficient radical scavengers (Vidari et al. 1971; Kim et al. 2004; Park et al. 2008). Quercetin and its methylated derivatives (31 and 32) have been reported to have strong activity against polio type 1 and Coxsackie B4 viruses both *in vitro* and *in vivo* (Tane et al. 2005).

Arylalkanoids

The diarylheptanoids (22–25) are groups of compounds which bears the 1,7-diphenylheptane skeletons as a special character. They were isolated for the first time from the seeds of *Aframomum letestuiianum*. Haining and She (2012) grouped them into linear and cyclic diarylheptanoids. They further classified linear diarylheptanoids into four groups: oxy bridges structures, flavonoid moiety, dimeric linear diarylheptanoids and those having unusual structures. Cyclic diarylheptanoids were grouped into 2-metaparacyclophanes and 10-metaparacyclophanes. Diarylheptanoids are known to exhibit a broad range of potent biological activities as anti-inflammatory, antioxidant, estrogenic, antihepatotoxic, leishmanicidal, melanogenesis, neuroprotective, antibacterial and antitumour. This group of compounds has also recently been shown to have an inhibitory activity against nitric oxide production in activated murine macrophages (Kim et al. 2005). Currently, ongoing investigations are being carried out on gingerdione (22), [6]-paradol (23), [6]-gingerol (24) and

[6]-shogaol (25). In a recent report, chloroform fraction of *A. melegueta* seeds yielded one new diarylheptanoid named 3-(S)-acetyl-1-(49-hydroxy-39,59-dimethoxyphenyl)-7-(30,40,50-trihydroxyphenyl)heptane (El-Halawany et al. 2014), in addition to four other diarylheptanoids previously isolated from *A. letestuiianum*, namely (4Z,6E)-5-hydroxy-1,7-bis(4-hydroxyphenyl)hepta-4,6-dien-3-one (26), letestuiianin A (27), B (28) and C (29) (Tane et al. 2005). [6]-Gingerol (24) and [6]-shogaol (25), also isolated from *A. melegueta*, have been reported to exhibit significant anti-feedant activity (Ukeh et al. 2009) (Figure 4). A summary of the isolated compounds from reviewed species and their biological activities are outlined in Table 1.

Toxicology

With the current emphasis on research and development of medicinal plants worldwide, it is important to have some information regarding the toxicity potentials and efficacies of plants utilized ethnobotanically to treat ailments. In ethnopharmacological studies of medicinal plants, a search in scientific literature should be made for known toxic properties of plants of interest before embarking on biological activity studies. However, where toxic effects are unavailable, the inclusion of cytotoxicity and other toxicity protocols in the study are useful in detecting potential toxicity. This strategy is applicable when screening plant extracts or isolated natural products for some other biological activities such as anti-infectious, anti-inflammatory, antioxidant, anti-diarrhoea and antiparasitic property (Shahid 2012).

Liver toxicity

Aframomum melegueta seed oil has the potential of ameliorating benign prostatic hyperplasia and cardiac dysfunction as indicated by testosterone, PSA, lipid profile and troponin levels. The LD₅₀ of 273.86 mg/kg body weight indicated mild toxicity with lower than normal Hb and RBC confirming the possibility of toxicity (Akpanabiatu et al. 2013). An ethanolic extract of *A. melegueta* seeds at an oral dose of 450–1500 mg/kg for 28 days in rats was noted to cause dose-dependent increase in liver weight with a mild increase in LDH and non-significant increases in AST. However, toxicity was not detected by histological examination (no detectable necrosis, steatohepatitis or cirrhosis) (Ilic et al. 2010). Methanolic extract of *A. melegueta* seeds was found to be potentially hepatotoxic ($p < 0.05$) at 300 mg/kg under prolonged ingestion at high dose. This was supported by the remarkable

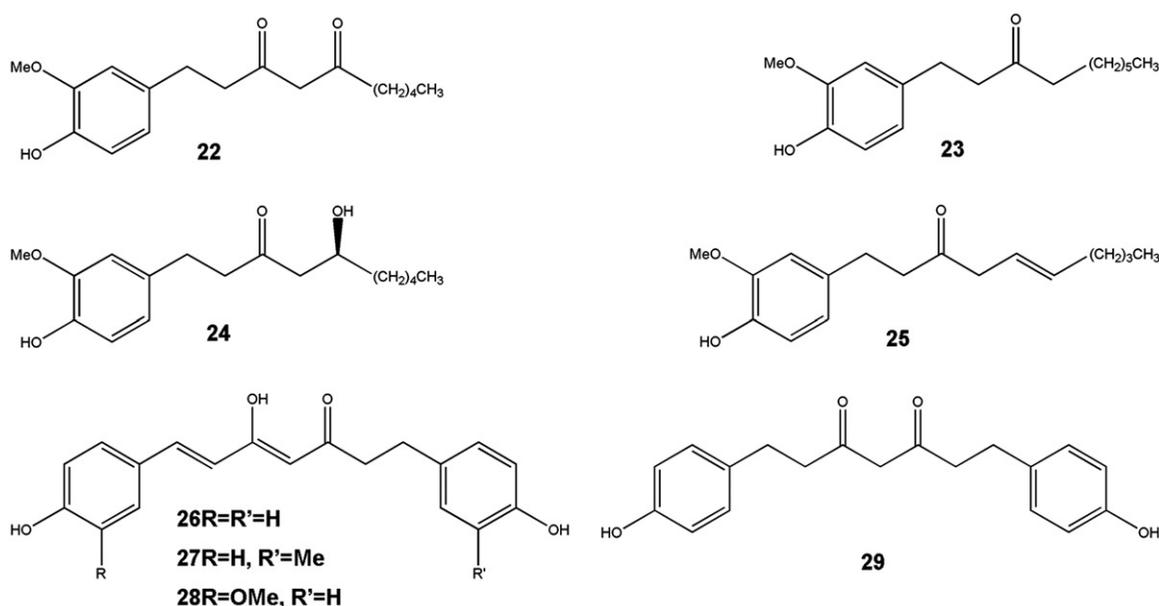


Figure 4. Structures of arylalkaloids.

Table 1. Summary of Aframomum species, isolated compounds and their biological activities.

Species	Compounds	Biological Activities
<i>A. polyanthum</i>	Terpenoids	Cytotoxic
<i>A. masuianum</i>	Aframodial	Antihypercholesterolemic
<i>A. keyseianum</i>		
<i>A. sulcatum</i>		
<i>A. arundinaeum</i>		
<i>A. latifolium</i>		
<i>A. longifolius</i>		
<i>A. aulacocarpos</i>	Aulacocarpinolide	Antibacterial Antiplasmodial
	Aulacocarpin A Aulacocarpin B	
<i>A. sceptrum</i>	Labda-8(17),12-dien-15,16-dial	Antifungal, Cytotoxic
<i>A. longifolius</i>		Antiplasmodial
<i>A. danielli</i>		
<i>A. sceptrum</i>	8β(17)-Epoxy-3β,7β-dihydroxylabd-12(E)-en-16,15-olide Methyl 8β(17)-epoxy-3β,7β,15-trihydroxylabd-12(E)-en-16-oate 3β,7β,8β,12ζ,17-pentahydroxylabdan-16,15-olide Coronarin B	Antiplasmodial Tripanosomal
<i>A. arundinaeum</i>	Galanolactone	Antifungal, cytotoxic
<i>A. sulcatum</i>		
<i>A. latifolium</i>		Antiplasmodial
	Galanals A Galanals B Narigenin 1E,5E-germacradien-4α-ol Norbislabdane sulcanal 12(E),8β(17)-Epoxy-11-hydroxy-12-labden-15,16-dial-11,15-hemiacetal 12(E),8β(17)-Epoxy-11-hydroxy-12-labden-15,16-dial-11,15-hemiacetal Methyl 14,15-epoxy-8(17), 12(E)-labdadiene-16-oate	
<i>A. danielli</i>		
<i>A. arundinaeum</i>		
<i>A. longifolius</i>	Acetal 8β(17)-epoxy-15,15-dimethoxylabd-12(E)-en-16-al Hemiacetal 15-hydroxy-15-methoxylabda-8(17),12(E)-dien-16-al 5E,10(14)-germacradien-1β,4β-diol	Antiplasmodial
<i>A. zambesiacum</i>	Sesquiterpenoids	
<i>A. sceptrum</i>	(+)-s-Nerolidol	
<i>A. escapum</i>		
<i>A. arundinaeum</i>	6,7-Epoxy-3(15)-caryophyllene (-)-α-Bisabolol	
	Flavanoids/phenols	
<i>A. giganteum</i>	kaempferol-3,7,4-trimethylether Quercetin-3,7,3',4'-tetramethylether Quercetin-3,7,4-trimethylether	Antibacterial, Antiviral, Anti-inflammatory
<i>A. letestuianum</i>	3-Acetoxy-5,7,4-trihydroxyflavone	

(continued)

Table 1. Continued

Species	Compounds	Biological Activities
<i>A. sceptrum</i>		
<i>A. prinosum</i>		
<i>A. handburyi</i>		
<i>A. letestuanum</i>	3-Acetoxy-5,4-dihydroxy-7- methoxyflavone	
<i>A. prinosum</i>		
<i>A. handburyi</i>		
<i>A. prinosum</i>	3,5-Dihydroxy-7,4-dimethoxyflavone	
<i>A. handburyi, A. sceptrum</i>	3-Acetoxy-5,4-dihydroxy-4- methoxyflavone	
	3,5,7,4-Tetrahydroflavone	
	Arylalkanooids	
<i>A. melegueta</i>	Gingerdione	Termite antifeedant
	6-Paradol	Antibacterial
	6-Gingerol	Antifungal
	6-Shogaol	
<i>A. letestuanum</i>	3-(<i>s</i>)-Acetyl-1-(49-hydroxy-39,59-dimethoxyphenyl) -7-(30,40,50-trihydroxyphenyl)heptanes (4Z,6E)-5-Hydroxy-1,7-bis-(4-hydroxyphenyl)hepta-4,6-dien-3-one	Anti-inflammatory Antihepatocic Antifungal, Antibacterial Antitumour
	Letestuanin A	
	Letestuanin B	
	Letestuanin C	

decrease in the mean body weight of all extract-treated rats, with elevations in serum AST, ALT, ALP and total bilirubin. There was also a decrease in the mean relative liver weight of test rats compared to the control as well as histopathological lesions on treated rat liver. However, low and high doses of aqueous extract of *A. melegueta* seeds have shown no toxicity in the histological observation of the adrenal glandular cells (Chinaka et al. 2014).

Pregnancy

A study in rats that used 50 mg of *A. melegueta* seeds mixed in 20 g rat chow (1% of feed; the food lasted for 4 days and then normal chow was fed to the rats) noted that the control group had an average litter size of seven. The experimental group fed with the seeds of *A. melegueta* failed to deliver pups although no other side-effects appeared apparent. This dose equated to 286–345 mg/kg in rats, and lower doses (0.5–2 mg injections) have since failed to adversely affect litter size. High doses have also been implicated in antifertility actions in females (Inegbenebor et al. 2009).

Conclusion

The genus *Aframomum* is a group of diverse tropical plants that has been used as an ethnomedicine since ancestral times. We have reported a number of studies that have been carried out on the uses and applications of *Aframomum* extracts and chemical constituents. It was observed that *A. giganteum* and *A. melegueta* are the most studied species. The whole plant of *A. giganteum* yielded mostly flavonoids, while hydroxyphenyl alkanoids have been reported from *A. melegueta* (Charles & Simon 1990). The information presented in this review on the phytochemistry and various pharmacological properties of the different extracts, essential oils and the constituents might provide incentive for proper evaluation of the use of the species in medicine. Test conducted in animal models for anti-inflammatory, analgesic, antinociceptive, reproductive capability, anticancer, gastroprotective and other biological activities have shown promising results without any adverse effect within normal stated doses. The major constituents (diterpenoids and sesquiterpenoids) of the essential oils have been

shown to produce precocious effects in insect control as well as in bacterial and fungal infection. Further conservation of the species at the genomic level, epigenomic level, transcriptional and post-transcriptional levels is essential for the sustainable development and utilization of *Aframomum* medicinal and food resources. The integration of biological systems and ‘omics’ techniques could dramatically enhance *Aframomum* research and development.

Disclosure statement

We declare no competing interest.

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