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Review Article

Overview of the Pharmacological Activities of *Aframomum melegueta*

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ABSTRACT

Aframomum melegueta (AM) is an herbaceous plant consumed as an edible spice and traditionally used to treat common ailments in West Africa, such as body pains, diarrhoea, sore throat, catarrh, congestion and rheumatism. Moreover, AM has been used to treat infectious diseases such as urinary tract infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterococcus faecalis, Staphylococcus saprophyticus, Proteus mirabilis,* methicillin-resistant *Staphylococcus aureus*, *Salmonella* spp, and *Shigella* spp. Based on current literature, different parts of the plant possess specific phytochemicals such as flavonoids, phenolic compounds, alkaloids, tannins, terpenoids, saponins, and cardiac glycosides that have healing potential and medicinal purposes. These phytochemicals exhibit anti-inflammatory, antimicrobial, anti-allergic, anti-clotting, anti-cancer, anti-diabetic and hepatoprotective effects. They also act as antioxidants to counteract free radicals, and immune enhancers as well as hormone modulators. However, research on medicinal properties of AM is still very limited. Therefore, more comprehensive studies need to be performed to elucidate the medicinal purposes of AM. This review summarises findings from previous studies on the pharmacological activities of AM.

Keywords: Aframomum melegueta, natural product, pharmacological activity, phytochemicals

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INTRODUCTION

Tropical plants have, since antiquity, been known to exhibit pharmacological effects, and utilising them for therapeutic purposes is far more economical than allopathic medicine. A report has suggested that the total number of terrestrial plant species is around 500,000 species globally (Corlett, 2016), consisting of an estimated 450,000 angiosperms (Pimm & Joppa, 2015), 1,000 gymnosperms (Christenhusz et al., 2011), 10,000 ferns (Ranker & Sundue, 2015), 1,300 lycophytes, 9,000 mosses (Magill, 2010), 250 hornworts (Villarreal et al., 2010) and 7,500 liverworts (Von Konrat et al., 2010). The practice of using plants to treat diseases has originated since antiquity, when people discovered that they harbour healing potentials (Ríos & Recio, 2005). The practice of using plants for the maintenance of health or treatment of illness is regarded as a type of "traditional medicine". The term "traditional medicine" is interchangeably used with "herbal medicine" or "natural medicine" (Gilani & Rahman, 2005).

In the same light, *Aframomum melegueta* (AM), from the family Zingiberaceae, is a shining example of an herbaceous plant used traditionally for treating ailments. The taxonomical classification of the plant is as follows: Plantae (kingdom), Tracheophyta (phylum), Liliopsida (class), Zingiberales (order), Zingiberaceae (family), *Aframomum* (genus) and *Aframomum melegueta* (species). This plant is also known as alligator pepper, grains of paradise, guinea pepper or melegueta pepper. It is native to tropical African countries such as Ghana, Nigeria, Liberia and Cameroon (Ngwoke et al., 2014), and is an important commercial crop in east African countries such as Ethiopia. It is cultivated in Indian house gardens as well (Khare, 2007). This plant can grow up to 1.5 m in height with orange-coloured lips and pinkish-orange upper flowers that can develop into fleshly and indehiscent pods. The size of the pods are 5-7 cm in length, are edible and contain numerous small, reddish brown seeds (Figure 1) with a pungent scent of ginger and cayenne pepper. The stem is short and covered with scars of fallen leaves. The leaves are about 30 cm long, 12 cm wide, and have close nerves underneath (Ilic et al., 2010; Van Harten, 1970).

A common condiment in West and North African cuisine, melegueta pepper or AM has been used as a spice for meats, sauces and soups. Traditionally, AM is mixed with other herbs for the treatment of common ailments such as body pains, diarrhoea, sore throat, catarrh, congestion and rheumatism in West Africa (Ajaiyeoba & Ekundayo, 1999). It is a perennial (seasonless) herbal plant that is often cultivated owing to its valuable pharmacological effects such as antimicrobial, hepato-protective, anti-cancer and anti-diabetic effects (Bravo, 1998; El-Halawany et al., 2014; Mohammed et al., 2017; Ngwoke et al., 2014). *In lieu* of mounting interest in the plant's bioactive effects, this review summarises some of the major pharmacological activities of AM.

Figure 1. Seeds of *Aframomum melegueta*

PHYTOCHEMICALS IN *Aframomum melegueta*

As with essentially all medicinal plants, the therapeutic effects of AM are generally due to the presence of secondary metabolites, known as phytochemicals (Alphonso & Saraf, 2012). Secondary metabolites are produced in response to stress factors and may not be involved in the normal growth and development of the plants. For example, hydroxylated coumarins are accumulated in carrots in response to fungal invasion (Darvill & Albersheim, 1984). Flavonoids are the most abundant compounds present in AM, which act as powerful antioxidants to alleviate medical conditions. Other compounds include phenols, saponins, tannins, ascorbic acid, niacin, riboflavin, thiamine, and minerals such as calcium, phosphorus, potassium, magnesium, sodium, iron, zinc, manganese and copper (Okwu, 2004, 2005). Table 1 shows the common phytochemicals present in AM and their common medicinal purposes. Active compounds that are identified in AM include gingerol, shogaol, paradol, rac-6-dihydroparadol and gingeredione, which demonstrate antimicrobial potential (Odetunde et al., 2015). Chemical structures of the active compounds are shown in Figure 2.

Table 1

Common phytochemicals in Aframomum melegueta (Okwu, 2004, 2005) and their potential medicinal properties

Phytochemicals	Potential medicinal properties
Flavonoids	Treat allergies (Castell et al., 2014), inflammation and intestinal troubles (Salaritabar et al., 2017) Counter free radicals, microbes (Cushnie & Lamb, 2005), ulcers (Mota et al., 2009), viruses, hepatoxins (Davila et al., 1989) Cause platelet aggregation (Faggio et al., 2017) Exhibit anti-cancer properties (Batra & Sharma, 2013)
Phenolic compounds	Promote wound healing (Song et al., 2017) and prevent infections (Machado et al., 2018) Exhibit anti-clotting, anti-inflammatory and antioxidant effects (Olas et al., 2008) Act as immune enhancer (Cuevas et al., 2013) as well as hormone modulator (Venugopal & Liu, 2012)
Alkaloids	Act as analgesic (Sutradhar et al., 2007), antispasmodic (Calixto et al., 1984) and bactericidal (Cushnie et al., 2014) agents

Table 1 *(Continue)*

Phytochemicals	Potential medicinal properties
Tannins	Hasten the healing of wounds and inhibit inflamed mucous membrane (Su et al., 2017)

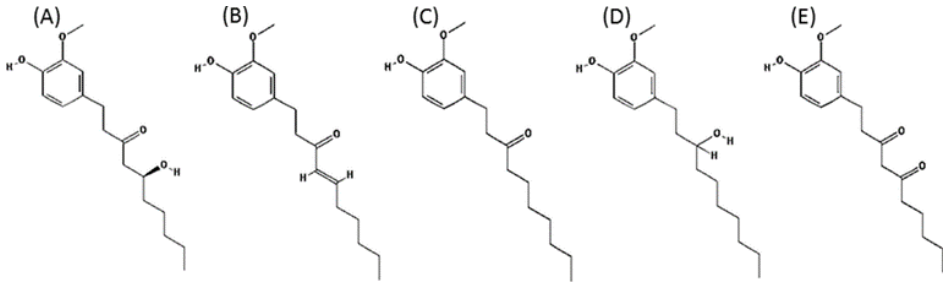

Figure 2. Chemical structures of (A) Gingerol, (B) Shogaol, (C) Paradol, (D) Rac-6-Dihydroparadol and (E) Gingeredione

Medicinal Properties of *Aframomum melegueta*

Antimicrobial Effect

One of the most significant pharmacological effects of AM is its antimicrobial activity. AM has been used to treat urinary tract as well as soft tissue infections, thus suggesting a strong antimicrobial potential of the plant (Ngwoke et al., 2014). Urinary tract infections (UTIs) are a serious public health problem affecting 150 million people worldwide (Stamm & Norrby, 2001). UTIs are commonly caused by several pathogens such as *Escherichia coli, Klebsiella pneumoniae, Enterococcus faecalis, Staphylococcus saprophyticus, Proteus mirabilis,* and *Staphylococcus aureus.* Some patients face recurrent UTIs and hence require repeated prescriptions of antibiotics. This potentially increases the antimicrobial resistance of the uro-pathogens, which in long term will greatly increase the economic burden for countering future infections (Flores-Mireles et al., 2015). As multidrug-resistant pathogens are a serious threat to the society, the antimicrobial activity of AM has been investigated as an alternative to antibiotics. Results show that AM is effective against some clinically important bacterial and fungal isolates such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Proteus* sp., *Salmonella* sp., *Bacillus* sp., *Escherichia coli*, *Klebsiella* sp., *Saccharomyces* sp., *Aspergillus* and *Candida* (Odetunde et al., 2015).

Virtually every part of AM possesses different phytochemicals that exert antimicrobial activity, which can be extracted by a repertoire of solvents. For instance, ethanol can be used to extract various phytochemicals in the seeds and leaves of AM. The ethanolic leaf extract contains phytochemicals such as tannins, alkaloids, saponins, steroids, cardiacglycoside and

terpenoids that have remarkable therapeutic actions in the treatment of gastrointestinal infections, nausea, respiratory problems, colds, fever, allergies, urinary tract infections and fungal infections. In short, ethanolic extract of AM has a broad spectrum of antimicrobial activity.

In a separate study, AM was found to inhibit the growth of *Salmonella* spp. and *Shigella* spp. (Doherty et al., 2010). In the acetone extract of AM's rhizomes, the presence of labdane diterpenoids such as zerumin A (Figure 3A) and (E)-labda-8(17),12-diene-15,16-dial (Figure 3B) can effectively kill Gram-positive bacteria such as *Escherichia coli* and *Listeria monocytogenes*. The labdane diterpenoids also inhibit the growth of MRSA, which is known to be resistant to most antibacterial agents. Furthermore, both zerumin A and (E)-labda-8(17),12-diene-15,16-dial exhibit greater antibacterial activity towards MRSA compared to the antibiotics such as ampicillin, gentamicin and vancomycin that are currently used clinically. Thus, they may represent potential antibacterial lead compounds (Ngwoke et al., 2014). Aqueous extraction of AM's rhizomes for phytochemicals, however, is not as effective as acetone extraction. Hence, acetone is a more appropriate solvent to be used for the extraction of diterpenoids from the rhizome of the plant (Eloff, 1998).

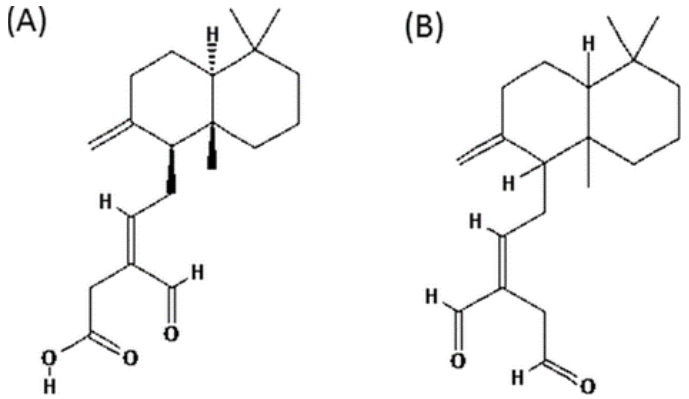

Figure 3. Chemical structures of (A) Zerumin A and (B) (E)-labda-8(17),12-diene-15,16-dial

Hepatoprotective Effect

The liver plays a vital role in metabolising toxic substances that enter the body, including alcohol, which is one of the major causes of liver diseases worldwide (Leggio & Lee, 2017). In the liver, alcohol is broken down into simpler end-products such as acetaldehyde to be easily eliminated from the body. Highly reactive molecules such as reactive oxygen species (ROS) generated during the metabolism of alcohol may contribute to the development of alcoholic liver diseases such as cirrhosis, simple steatosis and acute alcoholic hepatitis. The reactive molecules can destroy the vital cell components in the liver through

oxidation (Dunn & Shah, 2016; Fernández-Checa et al., 1997). Consequently, oxidative stress accumulates in cells from the imbalance between oxidants and antioxidants. Excessive oxidants damage the mitochondria, thus diminishing energy production (Fernández-Checa et al., 1997). Therefore, excessive alcohol consumption affects the health of the liver as well as that of other organs (Nordmann et al., 1992). Alcohol toxicity causes acute liver disease, and prolonged frequent consumption may lead to chronic liver diseases (Cederbaum et al., 2009).

On the other hand, chemical solvents such as carbon tetrachloride (CCl_4) used in the lab causes liver toxicity upon excessive exposure. CCl_4 can induce apoptosis of hepatocytes, and the oxidative stress and generation of free radicals may further harshen the CCl_4-induced liver injury (El-Halawany et al., 2014). Excessive alcohol consumption and inhalation of chemical solvents like CCl_4 can lead to significant elevation of serum alanine aminotransferases (ALT), aspartate aminotransferases and triglyceride levels, as well as a decrease in glutathione (GSH) and superoxide dismutase (Nwozo & Oyinloye, 2011). Tumour necrosis factor alpha (TNF-α) and interleukin-1 beta (IL-1β) levels are increased if the liver is inflamed (El-Halawany et al., 2014).

The humble seeds of the melegueta pepper have been proven to reverse such toxic effects. Its hepatoprotective effect is evaluated based on the changes in ALT, GSH, thiobarbituric acid reactive substances, TNF-α, IL-1β levels and activities of some enzymes such as caspase 3 and 9 (El-Halawany et al., 2014). Phytochemicals such as phenols and flavonoids that are present in the aqueous seed extract of AM were shown to have hepatoprotective effects (Nwozo & Oyinloye, 2011). These phytochemicals possess antioxidant properties which neutralise liver-damaging free radicals and reactive oxygen species (Choi et al., 2006). Methanolic and chloroform seed extracts of AM also exhibit similar effects. Compounds present in the extract include 3-(*S*)-acetyl-1-(4′-hydroxy-3′, 5′-dimethoxyphenyl)-7-(3″,4″,5″-trihydroxyphenyl) heptane and dihydrogingerenone (Figure 4) that can supress TNF-α and IL-1β levels in the body. These compounds impede the reduction of GSH by trapping free radicals arising from liver hepatocytes. In addition, these compounds also lower the levels of ALT, TNF-α, IL-1β as well as caspases 3 and 9. Apoptosis of hepatocytes induced by CCl_4 is also inhibited (El-Halawany et al., 2014). In short, the hepatoprotective effect of AM is due to its ability to suppress inflammatory responses and apoptosis, as well as the ability to forage free radicals.

Although significant in effect, the number of bioactive compounds found to contribute to the hepatoprotective effect in AM are quite limited in current literature. Hence, concerted efforts to extract and screen compounds from the plant for their biological activities and their effects should be expanded and its active metabolites tested *in vivo*. Different solvents might be used for extraction of different active compounds.

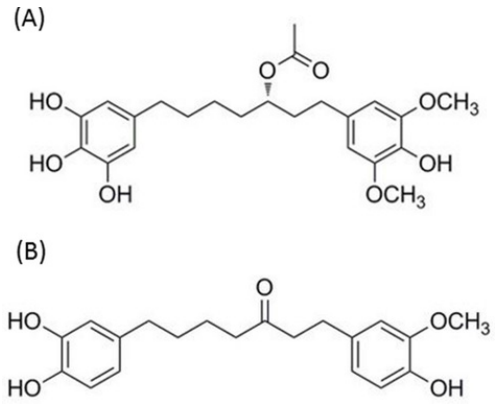

Figure 4. Chemical structures of (A) 3-(S)-acetyl-1-(4'-hydroxy-3',5'-dimethoxyphenyl)-7-(3",4",5"-trihydroxyphenyl) heptane and (B) Dihydrogingerenone

Anti-cancer Effect

The legendary cancer-battling antioxidants, flavonoids, have been found in relative abundance in AM (Doherty et al., 2010). Flavonoids are commonly reported to possess anti-carcinogenic and anti-mutagenic effects (Aranganathan & Nalini, 2013) in which they interfere with the development of malignant tumours by inhibiting the expression of mutant genes, inactivating carcinogens and enzymes that are involved in the activation of pro-carcinogens, as well as activating enzymatic systems that are involved in the detoxification of xenobiotics (Bravo, 1998). Flavonoids also inhibit the initiation, promotion and progression of tumours (Okwu, 2005; Urquiaga & Leighton, 2000). Quercetin, a flavonoid which can decelerate the development of tumours (Clifford et al., 1996), was also found to be present in the AM extract (Adefegha & Oboh, 2012). Although past studies have suggested that flavonoids isolated from various plants are effective against cancer cells, there is limited work on flavonoids isolated from AM. In a previous study, evidence showed that AM extracts were effective against pancreatic cancer (Dibwe et al., 2012).

Other supporting evidence includes a study by Kuete et al. (2011) who showed that the AM extract exerted significant inhibitory activities on human pancreatic cancer and leukaemia cell lines. Phytochemical investigations revealed the presence of (-)-buplerol, (-)-arctigenin, (E)-14-hydroxy-15-norlabda-8(17), 12-dien-16-al, labda-8(17),12-dien-15,16-dial, 16-oxo-8(17),12(E)-labdadien-15-oic acid, 5-hydroxy-7-methoxyflavone and apigenin in the extract. Among the list, (-)-arctigenin and (-)-buplerol showed the capacity to trigger apoptosis in pancreatic cancer cells (Dibwe et al., 2015).

The anti-cancer ability of AM may not be attributed to flavonoids alone. Paradols, common plant phenolic compounds, are also found to exert anti-cancer effects by inducing apoptosis in human pro-myelocytic leukaemia (HL-60) cells. The effect is due to the presence of a vanillyl moiety and ketone functional group in the compound. Additionally, paradols can also suppress tumour promotion of the skin *in vitro* (Chung et al., 2001).

Discovery of bioactive compounds that have anti-cancer potential from AM is very limited. Hence, the identification of novel anti-cancer compounds from AM and investigation on their mechanisms of action may be an area for further exploration.

Furthermore, utilisation of different solvents or extraction methods might be useful in isolating novel compounds from the plant.

Anti-diabetic Effect

In addition to its repertoire of therapeutic effects, AM may also prove its worth in combating metabolic disorders such as Type 2 diabetes. In this condition, the body resists the physiological effect of insulin. Therefore, too much insulin will remain in the blood for extended periods of time, causing the pancreas unable to secrete more insulin to control the glucose level in the blood. As a consequence, postprandial hyperglycaemia ensues (Gastaldelli, 2011).

A myriad of compounds found in AM such as 6-paradol, 6-shagaol, 6-gingerol, oleanolic acid and acarbose exert an anti-diabetic effect by inhibiting enzymes such as α-amylase and α-glucosidase. These enzymes are responsible for digestion and break down of the carbohydrates and polysaccharides from food into simple sugars to increase blood glucose levels. Among the compounds, 6-gingerol and oleanolic acid are more effective in inhibiting the enzymes (Mohammed et al., 2017). Based on the current evidence, AM is suitable for consumption by diabetic patients.

Anti-inflammatory Effect

Fascinatingly, AM extract has been known to reduce fat and even relieve painful arthritis when it is used as a massage oil (Odetunde et al., 2015). Meanwhile, the ethanolic seed extract contains phytochemicals such as tannins, saponins, flavonoids, steroids, terpernoids, cardiac glycosides and alkaloids that possess antimicrobial and anti-inflammatory effects (Doherty et al., 2010; Okwu, 2004). Okoli et al. (2007) provided evidence that the methanolic AM extract and its fraction contained alkaloids, glycosides, tannins, flavonoids, sterols and resins, with alkaloids and tannins as the major compounds. Both the extract and fraction showed potential systemic anti-inflammatory activity, as they inhibited rat paw oedema induced by egg albumin.

To support this claim, Ilic et al. (2014) reported that the ethanolic AM extract inhibited cyclooxygenase-2 (COX-2). Compounds that inhibit COX-2 activity are capable of reducing inflammatory responses (Seibert & Masferrer, 1994). The most active COX-2 inhibitory compound in the AM extract was [6]-paradol, while [6]-shogaol was found to inhibit expression of a pro-inflammatory gene, interleukin-1 beta (IL-1β). Results from the paw oedema model showed that the AM crude extract and its active compounds [6]-paradol, [6]-gingerol and [6]-shogaol significantly reduced inflammation in rats.

In another study utilising the aqueous seed extract of AM, sub-chronic inflammation was induced by 2% formaldehyde or 6% nystatin, while chronic inflammation was induced by carrageenan in rats. The results revealed that AM extract significantly reduced oedema induced by formaldehye and nystatin. Furthermore, it reduced the exudate induced by carrageenan (Umukoro & Ashorobi, 2005). El-Halawany et al.

(2014) suggested that the anti-inflammatory potential of AM might be due to its ability to downregulate cytokines such as TNF-α and IL-1β.

The present studies utilised ethanol, methanol and water for the extraction of compounds from AM. The role of hexane, ethyl acetate, and other alternative solvents is worth exploring as it may yield yet-to-be discovered active compounds from the plant.

Haematopoietic Effect

Another lesser-known finding is the influence of AM on blood cell production. When the methanolic seed extract of AM was administered to 2,4-dinitrophenylhydrazine-induced anaemic rats, the treatment showed an increase in haemoglobin levels and platelet count, indicating its erythropoietic potential in treating anaemia (Omoboyowa et al., 2017). Paradoxically, higher doses of the extract have previously been observed to be haematotoxic (Akpanabiatu et al., 2013), and thus the administered dose should be selected with caution.

CONCLUSION

Based on available evidence, AM consists of several phytochemicals that exert beneficial pharmacological activities. For instance, the presence of flavonoids, tannins, alkaloids, saponins, steroids, cardiac glycosides, terpenoids, labdane diterpenoids such as zerumin A and (E)-labda-8(17),12-diene-15,16-dial exhibit significant antimicrobial effects, with some even more effective than antibiotics. Moreover, compounds such as 3-(*S*)-acetyl-1-(4′-hydroxy-3′,5′-dimethoxyphenyl)-7-(3″,4″,5″-trihydroxyphenyl) heptane and dihydrogingerenone demonstrate hepatoprotective effects. Furthermore, AM phytochemicals such as flavonoids, paradols and phenolic compounds exert anti-cancer effects on oral squamous carcinoma and pro-myelocytic leukaemia. Finally, compounds such as 6-paradol, 6-shagaol, 6-gingerol, oleanolic acid and acarbose exhibit anti-diabetic effects by inhibiting the enzymes that metabolise carbohydrates into glucose. In summary, AM harbours an increasing inventory of health benefits and may serve as a source of potential alternative medicines for various disease states.

Despite its vast potential, current literature on the pharmacological effects of AM is very limited. Therefore, detailed studies on the various anatomical parts of AM could be systemically performed, and specific ranges of solvents or extraction methods could be used to maximise the mining of bioactive compounds from the plant. In addition, its effects on other biological activities such as immunomodulation could be explored, as AM is rich in phenolic compounds that may potentially contribute to such effect. More importantly, toxicological studies should be implemented prior to enlisting AM as a possible source of therapeutic drugs.

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