

Review

Aframomum melegueta K. Schum. (Grains of Paradise) and Its Therapeutic Applications

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Abstract: Grains of Paradise (*Aframomum melegueta* K. Schum), also known as Alligator pepper or Guinea pepper, is a tropical plant from the genus *Aframomum* K. Schum of the ginger family Zingiberaceae. This plant is native to West Africa and is widely distributed across the tropical coastal regions of West and Central African countries. In African traditional medicine, Grains of Paradise have extensive applications, and they are still used. Several phytochemical studies on *A. melegueta* revealed the presence of alkaloids, diarylheptanoids, flavonoids, lignans, phenolics and polyphenolics, saponins, stilbenoids, terpenes, vanilloid compounds, as well as vitamins and minerals. The crude extracts, fractions, and purified compounds from *A. melegueta* possess biological activities, e.g., antidiabetic, anti-inflammatory, antimicrobial, antioxidant, cytotoxic, hepatoprotective, hypotensive, and insecticidal properties, and some of these activities have been shown to have therapeutic relevance. This mini-review appraises the literature, recently published on the therapeutic relevance of *A. melegueta*, and incorporates its geographical distribution, taxonomy, cultivation methods, historical and cultural significance, and phytochemical composition.

Keywords: *Aframomum melegueta*; Zingiberaceae; Grains of Paradise; traditional medicine; therapeutic applications; anti-inflammatory; anti-obesity; antioxidant; toxicity

1. Introduction

Grains of Paradise (*Aframomum melegueta* K. Schum) (Figure 1), also known as Alligator pepper or Guinea pepper, is a tropical plant from the genus *Aframomum* K. Schum of the ginger family Zingiberaceae [1–3]. This herbaceous plant is native to West Africa and produces a spicy edible fruit with a long history in culinary use, for adding flavour to various dishes (as a substitute for black pepper) and alcoholic beverages.



Figure 1. *Aframomum melegueta* K. Schum: the whole plant is on the left and the seeds are on the right.



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Historically, Melegueta pepper was the common name for *A melegueta*, and the name has its links to the ancient West African Empire of Melle (Mali), formerly located around the upper Niger region. The empire was used by the Mandigos as a trade route for this spice. The earliest recorded mention of the Melegueta pepper in Europe was in 1214 at a festival in Treviso, Italy [2]. Grains of Paradise have played a significant role in traditional medicine and have been used as an aphrodisiac, a stimulant, and to treat several ailments [1,3]. In recent times, modern research has highlighted the potential health benefits of the seeds, prompting renewed interest and further exploration. This mini-review appraises the literature published on the therapeutic relevance of *A. melegueta* and incorporates its geographical distribution, taxonomy, cultivation methods, historical and cultural significance, and phytochemical composition.

2. Methods

The method involved a review of historical books and a search of several academic databases, including Google Scholar, NIL, PubMed, ScienceDirect, SAGE, ResearchGate, JSTOR, Semantic Scholar, AJOL, and the Liverpool John Moores University (LJMU) Library Discovery tool. The search focused on relevant research articles and literature related to *A. melegueta* (Grains of Paradise) and its therapeutic applications. The keywords and search terms used were *Aframomum melegueta*, Grains of Paradise, Alligator pepper, Grains of Paradise seeds, Clinical use of Grains of Paradise, West African spices in traditional medicine, gingerols, flavonoids, phenols, and therapeutic benefits of *Aframomum*.

The search inclusion and exclusion criteria were as follows: studies that focused on their use in traditional medicine, Historical application, phytochemical composition, pharmacological properties, and ethnomedicine were included; to ensure relevance and recent studies, articles published within the last 10 years were prioritised, and articles with outdated references or studies with limited relevance to the research were excluded.

Data extraction and analysis involved reviewing selected studies and comparing them to identify trends, advancements, and gaps in research on *A. melegueta*. Emphasis was placed on articles on phytochemical profiling, bioactive compounds, and their pharmacological effects, including anti-inflammatory, antioxidant, and anti-obesity effects, as the key focus. The findings from older studies were contrasted with more recent research from the past ten years to determine how the scientific understanding and applications of *A. melegueta* have evolved.

3. Geographical Distribution

Aframomum melegueta is native to western Africa and widely distributed across the tropical coastal region of western and central African countries, specially within the swampy habitats of the coastal forest zones, including Angola, Benin, Cameroon, Congo, Gabon, Gambia, Ghana, Ivory Coast, Liberia, Nigeria, Sierra Leone, Togo, and Zaire, and was introduced to the Caribbean and southern America (Demerara) including Brazil, French Guiana, Guyana, Trinidad-Tobago and Windward Island, by Europeans during the trade of enslaved Africans [3,4]. This plant is also reported to grow in East Africa (Burundi and Uganda). Generally, this plant thrives in hot, humid, and tropical climates, often found in shaded, swampy areas of the rainforest, and it is usually cultivated in agroforestry systems alongside other crops such as oil palms and cocoa.

4. Botanical Description and Taxonomy

Aframomum melegueta is the homotypic synonym of *Amomum melegueta* Roscoe, the name of which was given by Williams Roscoe in 1828 when he first described the species in his book 'Monandrian of Plants' [5]. However, the name *Amomum melegueta* was later found to be invalid, "nom. illeg." indicating that the name is illegitimate according to the rules of botanical nomenclature. The correct name, *Aframomum melegueta* K. Schum, was established by Karl Moritz Schumann.

Aframomum melegueta is a palm-like perennial plant, and 1.0 to 1.8 metres tall. Its smooth, narrow-lanceolate leaves measure about 23 cm, and the surface root system has a scaly rhizome [6]. The plant produces stigma, trumpet-shaped purple blooms with a single stamen. The mature fruit forms red ovoid pods measuring 12.5 × 5.0 cm. Inside the pods are several firm, reddish-brown, shiny seeds, about 3 mm in diameter. The mature fruits are carefully harvested and left to dry completely. The pods are then opened to reveal seeds encased in thin dried skin with bumps that resemble an alligator's back. This appearance suggests why it is commonly called "Alligator pepper." The seeds have a peppery, spicy, and slightly bitter flavour, along with a robust, pungent, and aromatic smell due to the aromatic ketone composition in the seed.

5. Cultivation

For the cultivation of *A. melegueta*, the optimal growing conditions include a tropical climate with warm temperatures (25–30 °C) and high humidity [7]. This plant is best planted during the rainy season (March–June), and partial shade and a well-drained, loamy soil enriched with organic matter are needed. Regular watering and the use of organic manure for soil enrichment are necessary to ensure proper germination and growth. It takes 8–12 months or slightly more to mature, depending on environmental factors. During harvesting, mature pods are carefully cut to avoid plant damage and are dried before seeds are collected and stored in an airtight container/sack. A single plant yields 10–15 pods annually, and 200 plants can produce 2000–3000 pods per year. Pods yield 15–20 kg of seeds, depending on size.

6. Historical and Cultural Significance

In the Middle Ages, the seeds of *A. melegueta* were highly valued for their health benefits and in the preparation of alcoholic drinks, including the famous drink ‘Hippocras’ (now known as mulled wine) for helping digestion after meals [8]. In the 13th century, Grains of Paradise were prescribed by the Physician Nicolas Myrepsus under the name Meveveras at the court of Emperor John III in Nicaea. Simon of Genoa also named the drug Melegete or Melegette. By 1245, it was sold in Lyons and used by the Welsh Physicians of Myddvai, who called it Grawn Paris. In 1358, it appeared in a Dutch tariff as Greyn Paradijs. Between 1359 and 1360, the spice under the name “Grainne de Paradis” was mentioned as one of those used by John, King of France, during his time in England [9]. The term “grana paradisi” (meaning grains of paradise) underscores the economic and cultural importance of these spices during the medieval period [10,11]. Historically, medieval spice traders might have propagated the myth that these spices were only grown in the Garden of Eden to make them appear rarer and, consequently, more valuable on the market.

Early European explorers, including Christopher Columbus, sailed to West Africa with the intention of breaking Venice’s near monopoly on the spice trade. They were in search of alternative sources of spices and found the Melegueta pepper. This discovery was so significant that the region, particularly what is now Liberia, was labelled the “Grain Coast” based on 18th- and 19th-century maps, as a result highlighting its importance in maritime trade [12].

Until the early 19th century, large quantities of Melegueta pepper were imported into England. The seeds were valued for flavouring, medicinal uses, and as a substitute for cardamom in the gin and beer industry [10]. However, in 1825, the British government imposed a heavy tax and banned their use in alcoholic drinks. As noted by Roscoe around 1825, this led to an almost total prohibition of their import. This drastic policy shift caused a sharp decline in the international trade of these seeds, reducing it to a fraction of its former scale. Its use today is mostly in veterinary and culinary use [10].

While international trade remains minimal, the Melegueta pepper continues to thrive in local West African markets. The plant, *A. melegueta*, is widely cultivated, and seeds remain a staple. Interestingly, the same species is still grown in parts of South America, where locals continue to use the seeds as a valuable ingredient in several dishes.

7. Ethnomedicinal Applications

In African traditional medicine, Grains of Paradise have extensive application, and they are still used [4]. The dried seeds are pulverised into powder or sometimes mixed with water and applied directly or mixed with concoctions to treat several illnesses, including stomach aches, pains, inflammation, and as a stimulant. In some parts of Africa, southern Nigeria, these seeds are used as part of ritual divination and employed in local trials to determine guilt and as part of baby-naming ceremonies. Among the eastern people of Nigeria, the seeds are served with kola nuts to entertain guests. In Ethnomedicine, traditional healing practices embrace a holistic approach deeply rooted in historical cultural beliefs and knowledge. In several parts of the world, Grains of Paradise have been used to treat various ailments and improve overall health [1–4]. The seeds are ground into powder or softened and used to prepare an anti-inflammatory agent, pain reliever, remedies for treating infections, indigestion, nausea, vomiting, and as a tonic for sexual arousal. Sometimes, the seeds are chewed to provide warmth during cold weather.

8. Phytochemistry

Several phytochemical studies on *Aframomum melegueta* revealed the presence of alkaloids (e.g., sparteine and theophylline), diarylheptanoids (e.g., letestuiainin A), flavonoids (e.g., kaempferol and its derivatives), lignans (e.g., arctigenin and buolerol), phenolics and polyphenolics (e.g., gallic acid, caffeic acid, catechin and ferulic

acid), saponins, stilbenoids (e.g., resveratrol), terpenes [e.g., (*E*)-14-hydroxy-15-norlabda-8(17),12-dien-16-al and 16-oxo-8(17),12(*E*)-labdadien-15-oic acid], vanilloid compounds (e.g., 6-gingerol, 6-paradol and 6-shogaol) as well as vitamins (e.g., ascorbic acid, niacin, riboflavin, and thiamine) and minerals (e.g., calcium, magnesium, sodium, phosphorus, potassium, iron, zinc, manganese, and copper) [13–22]. The essential oil of this plant contains various terpenoidal compounds, e.g., 3-caryophyllene, cedrene, *p*-cymene, humulene, linalool, and nerolidol [23].

Most reported phytochemical studies are preliminary qualitative studies without the isolation and spectroscopic identification of individual compounds; only the structural classes, e.g., alkaloids, flavonoids, and saponins, were detected. However, there are a few studies where the isolation and identification of individual compounds were undertaken. Angustifoline, caffeine, indicine-*N*-oxide, lupanine, senkirkine, sparteine, theophylline, and undulatine are among the reported major alkaloidal compounds from *A. melegueta* (Figure 2).

This plant produces diarylheptanoids, and letestuiainin A appears to be one of the major ones (Figure 3). Other diarylheptanoids isolated from this plant are dihydrogingerenones A and C, 1,7-bis(3,4-dihydroxy-5-methoxyphenyl)-heptane-3,5-diyl-diacetate, 3-(*S*)-acetyl-1-(4',5'-dihydroxy-3'-methoxyphenyl)-7-(3'',4''-dihydroxyphenyl)-heptane, 3,5-diacetoxy-1-(3',4'-dihydroxyphenyl)-7-(3'',4''-dihydroxy-5''-methoxyphenyl)-heptane, 1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)-3-heptanone and (4*E*)-1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)-(4*E*)-4-hepten-3-one.

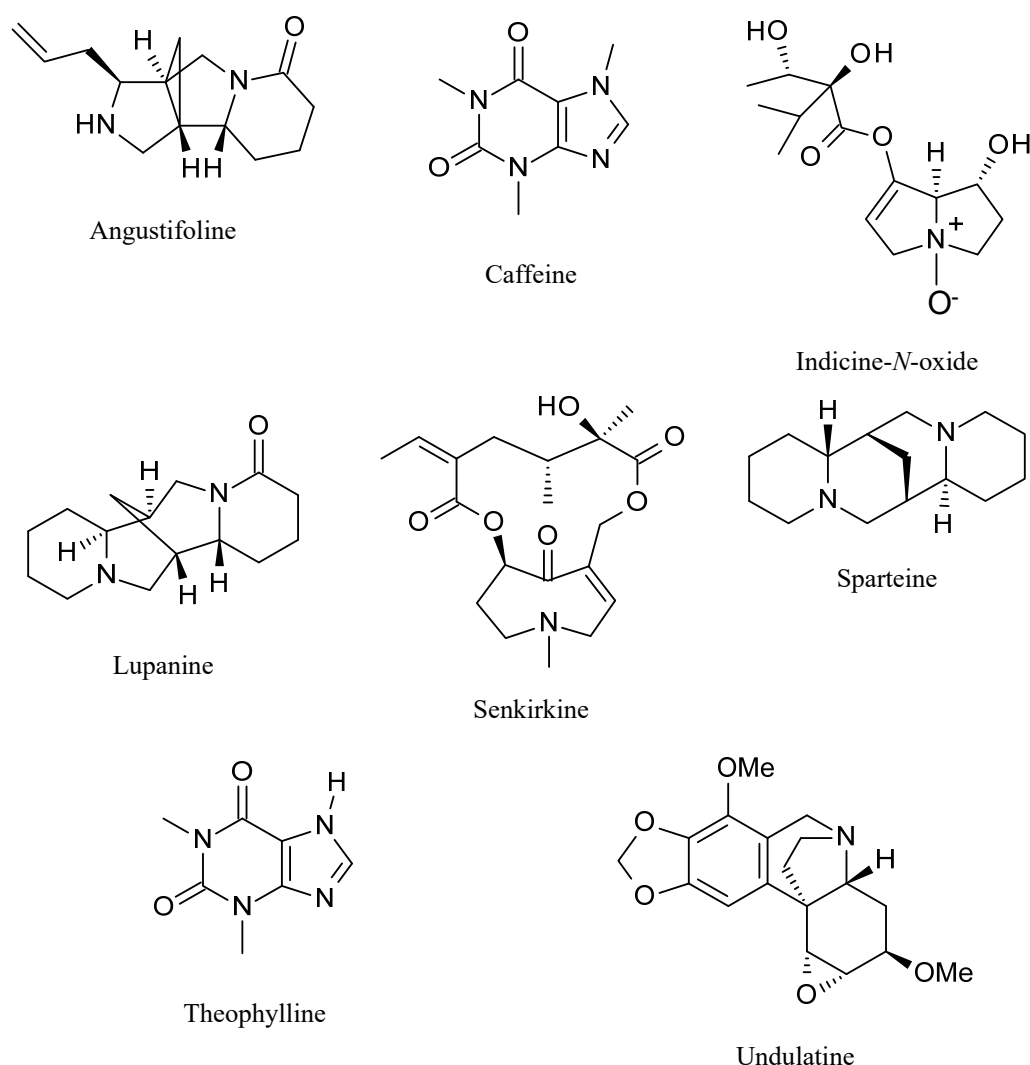


Figure 2. Major alkaloids of *A. melegueta*.

Flavonoids isolated from this species predominantly belong to apigenin, kaempferol, and quercetin derivatives, including their glycosides, e.g., rutin (Figure 3), and quercetin is the most abundant flavonoid in *A. melegueta* [22]. Highly methoxylated flavonols, e.g., kaempferol 3,7,4'-trimethylether, quercetin 3,7,3',4'-tetramethylether, and quercetin 3,7,4'-trimethylether are also biosynthesised by this plant [18]. Flavonoids in this plant constitute one of the major classes of bioactive compounds that contribute to the medicinal properties of this plant.

Arctigenin and buplerol are two main lignans, which are dimeric phenylpropane derivatives, reported from *A. melegueta*, while this species is rich in simple phenolics and polyphenolic compounds, including phenolic acids, e.g., caffeic acid, ferulic acid, and gallic acid, and stilbenoids, e.g., resveratrol (Figure 4). Catechin and epicatechin derivatives form the major group of polyphenolic compounds found in this plant [18]. Only a couple of labdane-type triterpenoidal compounds, e.g., (*E*)-14-hydroxy-15-norlabda-8(17),12-dien-16-al and 16-oxo-8(17),12(*E*)-labdadien-15-oic acid, were reported from *A. melegueta*. Although qualitative phytochemical investigation on *A. melegueta* detected the presence of saponins in this plant, there are no reports on the isolation and identification of any individual saponin.

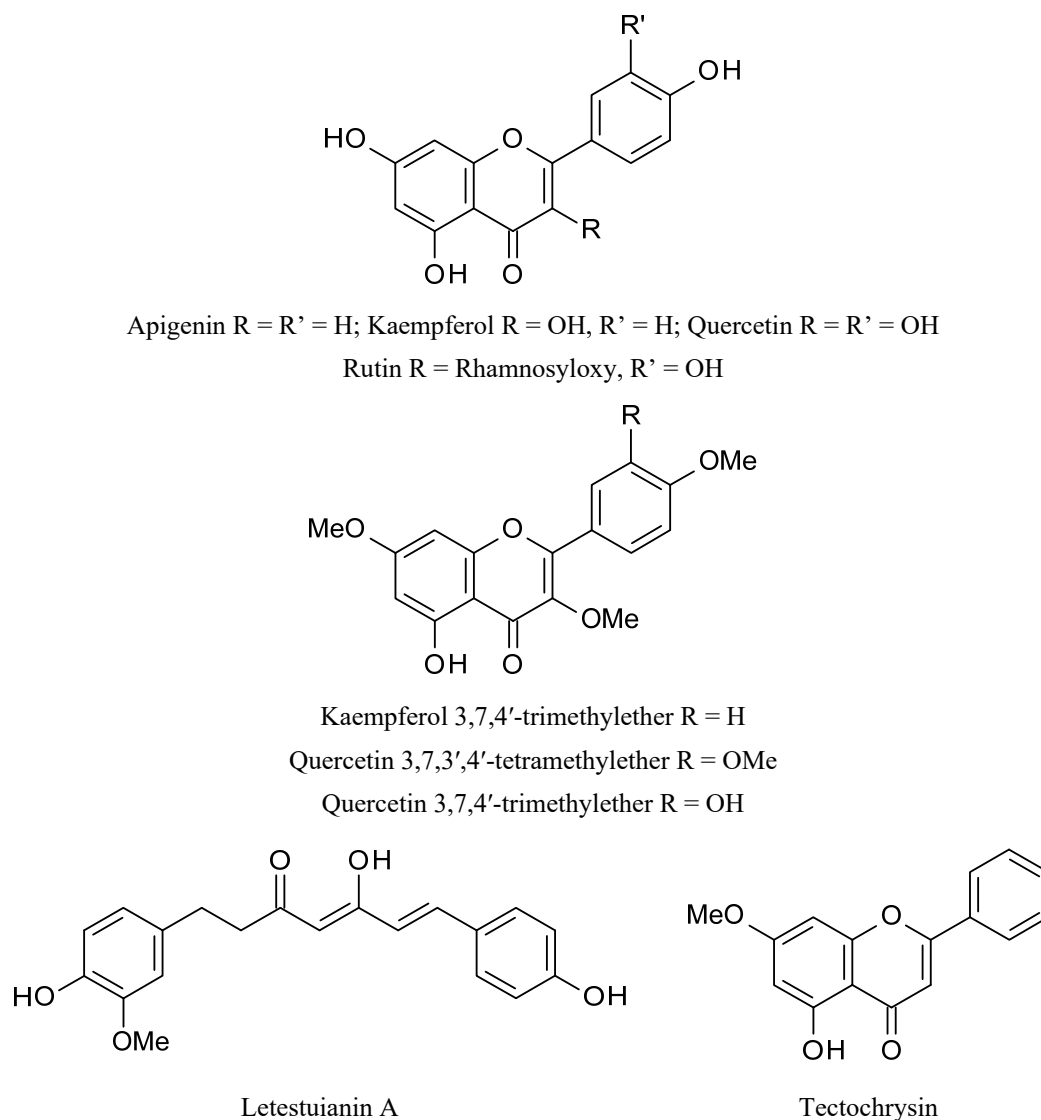


Figure 3. Major diarylheptanoid and flavonoids of *A. melegueta*.

Gingerol- and shogaol-type vanilloid compounds are widespread in plants from the Zingiberaceae family; *A. melegueta* is no exception. About 40 different vanilloid compounds have been reported from *A. melegueta* to date [18], and 1-(4'-hydroxy-3'-methoxyphenyl)-decan-3-ol, 1-(4'-hydroxy-3'-methoxyphenyl)-3-octen-5-one, 6-gingerol, 6-paradol, and 6-shogaol (Figure 5) are the major vanilloid compounds in this species.

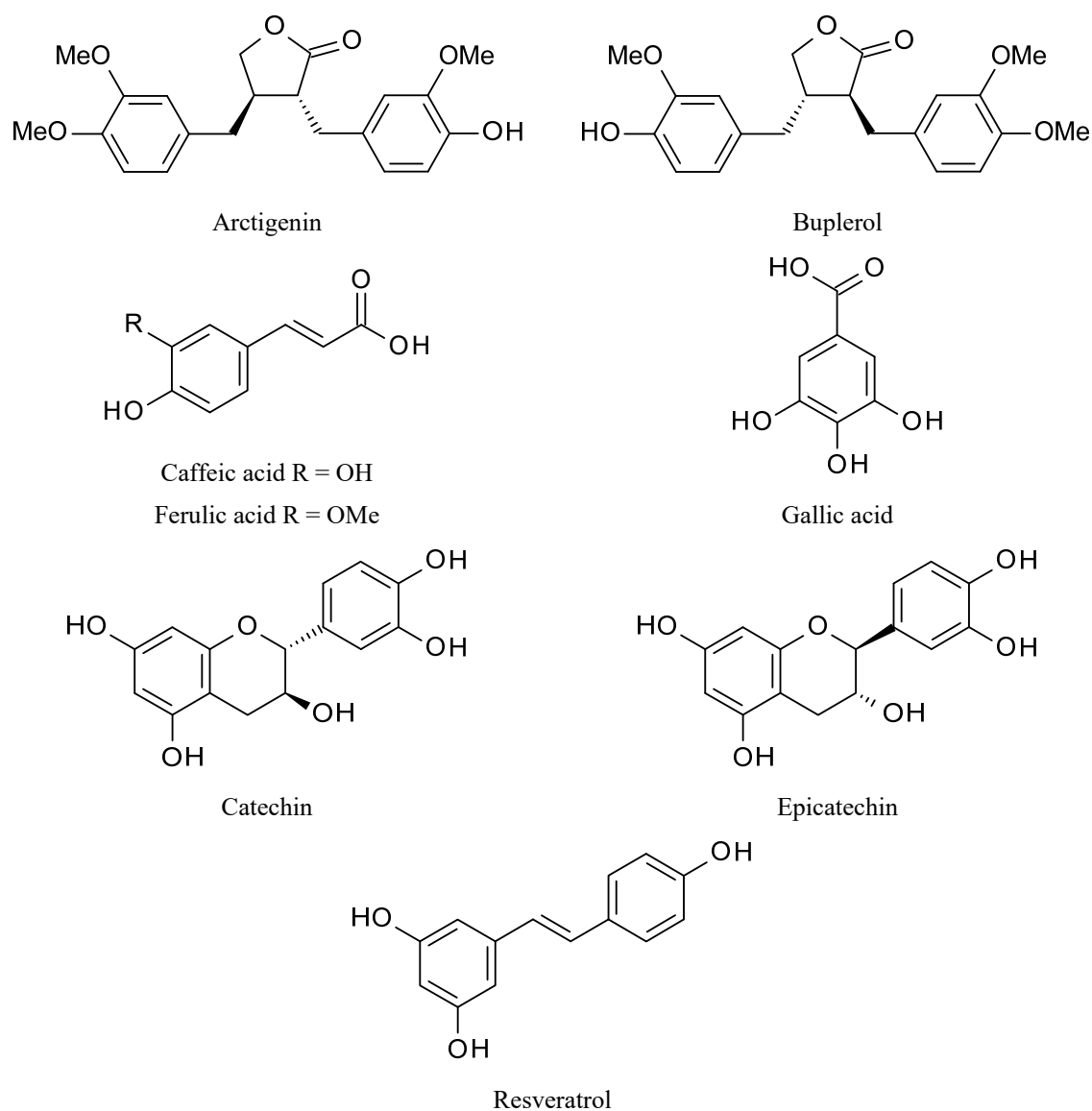


Figure 4. Lignans and major phenolic and polyphenolic compounds of *A. melegueta*.

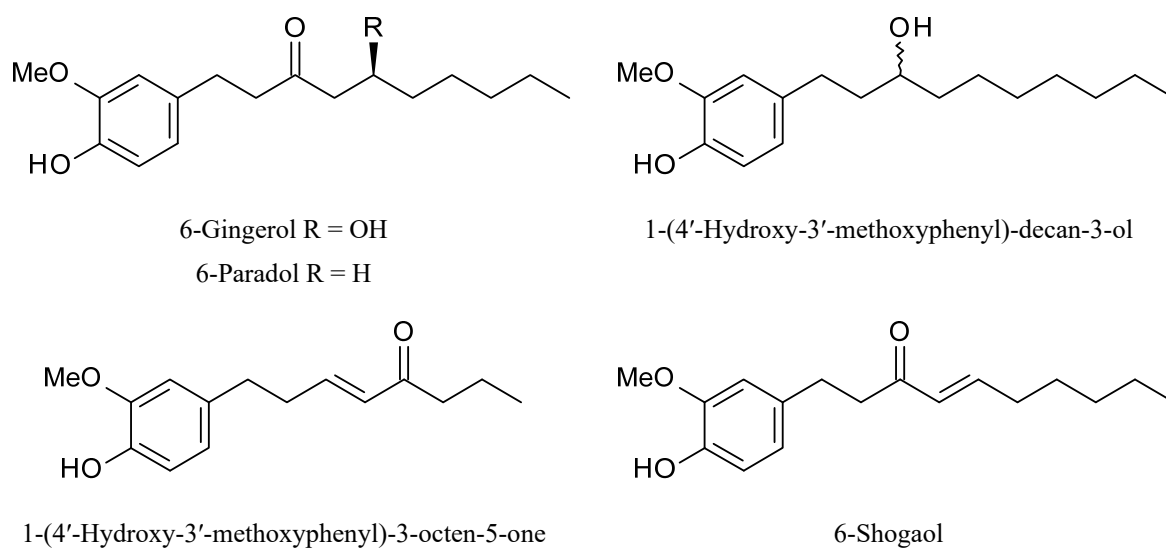
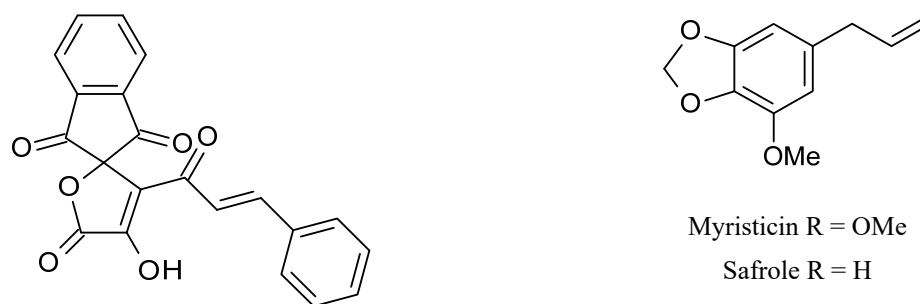


Figure 5. Major vanilloid compounds of *A. melegueta*.

In addition to the above major classes of secondary metabolites, there are also a few other compounds isolated from this plant, including 4-cinnamoyl-3-hydroxy-spiro[furan-5,2-(1'H)-indene]-1',2,3 '(2'H,5H)-trione) and phenylpropene derivatives, myristicin, and safrole (Figure 6).



4-Cinnamoyl-3-hydroxy-spiro[furan-5,2'-(1'H)-indene]-1',2,3 '(2' H,5H)-trione)

Figure 6. Miscellaneous compounds of *A. melegueta*.

9. Therapeutic Applications

The crude extracts, fractions, and purified compounds from *A. melegueta* possess biological activities, e.g., antidiabetic, anti-inflammatory, antimicrobial, antioxidant, cytotoxic, hepatoprotective, hypotensive, and insecticidal properties. However, not all those bioactivities could be classified as ‘therapeutically’ relevant [18]. Nonetheless, some of those bioactivities have therapeutic relevance as demonstrated by several studies. Major potential therapeutic applications of *A. melegueta* are outlined below.

9.1. Anti-Inflammatory Effects

Inflammation is a vital physiological response to tissue damage or infection, mediated by several signalling pathways [24]. Any plant materials, their extracts, or isolated compounds that possess anti-inflammatory properties can be therapeutically relevant to various disease states. *A. melegueta* has been shown to demonstrate anti-inflammatory properties mediated through inhibition of cyclooxygenase-2 (COX-2 enzyme), which is considered a key target for anti-inflammatory drugs [25]. Vanilloid compounds, e.g., gingerols and their analogues, isolated from the seeds of *A. melegueta*, demonstrated anti-inflammatory properties by inhibiting the synthesis of COX-2 enzyme and prostaglandins [26]. These vanilloid compounds interfere with the production of pro-inflammatory mediators, and this inhibition leads to a reduction in pain and inflammation. An extract of *A. melegueta* seeds from Abidjan, obtained with 95% EtOH, was shown to possess anti-inflammatory agents like 6-gingerol, 6-paradol, and 6-shogaol (Figure 4) [27]. *In vitro* COX-2 inhibitory activity of the seed extracts of this plant was comparable to that of Vioxx[®], an NSAID known to inhibit COX-2, with the extract achieving 76% inhibition, closely approaching 87% with Vioxx[®]. When this activity was assessed with some of the major compounds of this plant, 6-paradol was found to exhibit the highest COX-2 inhibitory effect at 91%, exceeding Vioxx[®], 6-shogaol, followed by a 68% inhibition, while 6-gingerol showed a modest 7% inhibition [27]. Anti-inflammatory activity of *A. melegueta* and its components was also tested *in vivo*, where the carrageenan-induced rat paw oedema model was employed [28]. An EtOH extract (dose of 1000 mg/kg) reduced oedema by 49%, which was comparable to the 43% reduction achieved by the positive control aspirin at 150 mg/kg. However, at a 500 mg/kg dose, the extracts exhibited a reduced anti-inflammatory effect, achieving 11% reduction in oedema. At a much lower dose of 150 mg/kg, purified compounds from this plant’s extracts displayed varying effects *in vivo*; 6-shogaol reduced oedema by 38%, 6-gingerol by 25%, and 6-paradol by 20%. This study suggested that Grains of Paradise extracts could exhibit *in vivo* anti-inflammatory activity, albeit it was not as effective as aspirin at comparable doses. Despite the lower efficacy of this plant and its compounds as anti-inflammatory agents, the findings corroborate the effectiveness of 6-shogaol, which showed better antioxidant and anti-inflammatory properties in comparison to other gingerols. The anti-inflammatory effects were found to be dose-dependent.

There are also several other studies published in the literature where vanilloids like 6-gingerol, 6-paradol, and 6-shogaol, three major components of *A. melegueta*, demonstrated significant anti-inflammatory activity, including activity in neuroinflammation and cerebral ischemia [29–36]. Considering the published literature on *in vitro* and *in vivo* studies with bioactive compounds from *A. melegueta*, some of these compounds clearly have

therapeutic potential as anti-inflammatory agents and could be considered useful templates for new anti-inflammatory drug development. The anti-inflammatory actions of these compounds not only involved COX-2 inhibition but also were mediated through other mechanisms, such as protecting dopaminergic neurons in Parkinson's disease models, and up-regulation of ROR γ T mRNA and protein, and the downregulation of FOXP3 mRNA and protein in a dextran sulfate sodium (DSS)-induced colitis [30,31]. The therapeutic potentials of gingerols, shogaols, and paradols, especially obtained from *Zingiber officinalis* Roscoe, in managing inflammation have recently been reviewed [32]; it was concluded that gingerols could alleviate inflammation given their ability to inhibit the activation of protein kinase B (Akt) and nuclear factor kappa B (NF- κ B) signaling pathways, causing a decrease in proinflammatory and an increase in anti-inflammatory cytokines. However, the bioavailability of these vanilloids is low, and therefore, it is necessary to develop new and more effective strategies for treatment using gingerols. One of the strategies could be nanotechnology-assisted delivery of these compounds.

9.2. Anti-Obesity Property

Obesity is a major global health concern that puts a significant strain on healthcare systems due to its strong link with chronic diseases such as diabetes, cardiovascular disease, and cancers [37–40]. It affects individuals of all ages and socioeconomic groups. World Obesity [39] predicts that the global economic impact of overweight and obesity will exceed \$4 trillion by 2035. There is a growing consensus on the urgent need for effective strategies to manage obesity and reduce its prevalence. The compounds from *A. melegueta* offer metabolic benefits, including enhancing energy expenditure and inhibiting excessive fat accumulation, which may contribute to weight management [41]. Previous research has identified 6-paradol as a key bioactive compound that activates brown adipose tissue (BAT) [42,43]. The effects of 6-paradol on high-fat diet-induced obese mice were compared with other vanilloids to examine its impact on body weight and fat reduction [43]. This study compared the anti-obesity potential of capsaicin (a transient receptor potential vanilloid-1-TRPV1 channel activator) with that of 6-paradol. The research demonstrated that 6-paradol effectively decreased visceral and subcutaneous fat in 2 weeks. 6-Paradol decreased hepatic triglycerides and total cholesterol, unlike 6-gingerol and 6-shogaol [43]. Sudeep et al. [44] conducted a double-blind study on 70 overweight individuals (BMI 25–30 kg/m² aged 20–50 years) receiving 250 mg of AferFit (*A. melegueta* extract) twice daily for 12 weeks [44]. The findings of the trial showed an 18.55% increase in energy expenditure ($p < 0.001$), likely due to BAT activation, significant visceral fat reduction ($p < 0.001$), as shown by CT (computed tomography) scan analysis, and a mean weight loss of 4.07 kg in the AferFit group compared to 0.81 kg in the placebo group. There were no adverse effects on liver and kidney function, confirming safety. These findings reinforce the potential of Grains of Paradise as a natural thermogenic agent with potential in obesity management through fat reduction and energy expenditure. However, more research is required in a larger population over an extended duration to explore its long-term efficacy and effectiveness in human trials. Anti-obesity potential of *A. melegueta* has recently been demonstrated using in vitro lipase inhibitory assay, which measured the ability of *A. melegueta* seed powder extract to inhibit the enzymatic hydrolysis of *p*-nitrophenyl palmitate, a synthetic substrate for lipase [45]. The anti-obesity potential of this plant was evident from its $40.18 \pm 2.33\%$ inhibition with an IC₅₀ of 0.04 mg/g of pancreatic lipase activity. Anti-obesity potential of *A. melegueta* seeds was also evident from the antihyperlipidemic activity observed in Triton X-100-induced hyperlipidemic rats [46].

Increasing adaptive thermogenesis through the activation of brown adipose tissue (BAT) is considered a practical strategy for preventing obesity and related disorders [42,43,47]. Ingestion of a single dose of 40 mg of an extract of *A. melegueta* seeds could trigger BAT thermogenesis in individuals with high but not in those with low BAT activity. This small-scale study using human volunteers tested the hypothesis that prolonged treatment with this plant might revive BAT in individuals who have lost active BAT. This study used fluorodeoxyglucose positron emission tomography and computed tomography (FDG-PET/CT) following 2-h cold exposure at 19 °C. The human subjects ingested *A. melegueta* extract (40 mg/d) or a placebo every day for 5 weeks. Before and after the treatment with either *A. melegueta* or placebo, their body composition and BAT-dependent cold-induced thermogenesis (CIT)-a non-invasive index of BAT were measured in a single-blinded, randomised, placebo-controlled crossover design. IT was observed that their whole-body resting energy expenditure at a thermoneutral condition remained unchanged following *A. melegueta* treatment. However, CIT after treatment was significantly higher in *A. melegueta*-treated individuals than in placebo-treated individuals. Body weight and fat-free mass did not change significantly following *A. melegueta* or placebo treatment. Notably, body fat percentage slightly but significantly decreased after *A. melegueta* treatment, but not after placebo treatment. These results suggested that repeated ingestion of *A. melegueta* could elevate adaptive thermogenesis through reactivation of BAT, thereby

reducing body fat in individuals with low BAT activity. Considering all the above findings, it can be stated that *A. melegueta* may be used as an acceptable therapeutic intervention in managing obesity.

9.3. Antioxidant Activity

Free radicals, or reactive oxygen species (ROS), are produced due to normal metabolic processes and are typically neutralised by the body's antioxidant systems [48,49]. However, when endogenous antioxidant defences are overwhelmed, oxidative stress occurs, thus leading to disruption of cellular redox balance and eventually oxidative cell damage. This imbalance plays a role in the subsequent development of inflammation and various chronic diseases, including cancer, neurodegenerative disorders, cardiovascular diseases, diabetes, and emphysema [48–51]. To mitigate cellular redox imbalance caused by excessive ROS, and to prevent oxidative stress-related diseases, an external supply of antioxidants is required, and plants play a vital role in supplying such antioxidants, e.g., vitamin C, phenolic compounds, including anthocyanins, and flavonoids [52]. *A. melegueta* is such a plant that is rich in antioxidant compounds, and several studies have demonstrated significant antioxidant activity of this plant and its isolated compounds [45,53–58]. The antioxidant property of this plant is attributed to its secondary metabolites, especially flavonoids, diarylheptanoids and other phenolic compounds, which function as free-radical scavengers by donating hydrogen atoms to neutralise ROS effectively reducing oxidative stress and preventing cellular damage. The antioxidant properties of *A. melegueta* seeds help prevent chronic diseases linked to oxidative stress, including cardiovascular diseases, cancers, and liver diseases [49].

A study conducted by Mounia et al. [19] provided insights into the safety profile, antioxidant efficacy, and bioactive components of *A. melegueta*, supporting its potential use in managing oxidative stress-related disorders. The study evaluated the seed extracts through *in vitro* [including the DPPH (2,2-diphenyl-1-picrylhydrazyl), ferric reducing power (FRP), and phosphomolybdate assays] and *in vivo* assays to assess free-radical-scavenging capacity. Key bioactive compounds identified in the EtOH and MeOH extracts of *A. melegueta*, e.g., caffeic acid, caffeine, catechin, coumarin, ferulic acid, gallic acid, quercetin, and rutin, are known natural antioxidants, and they support claims of the therapeutic benefits and use of this plant in traditional medicine. Both extracts could reduce lipid peroxidation levels *in vivo*, indicating their ability to mitigate oxidative damage in biological systems. Additionally, the extracts showed a significant protective effect against hydrogen peroxide (H₂O₂)-induced oxidative haemolysis in a dose-dependent manner. The highest percentage inhibition was observed at 100 µg/mL, EtOH extract at 91.35%, MeOH extract at 88.48%, and ascorbic acid (positive control) 81.25%, indicating their role in protecting red blood cells from oxidative stress. Both extracts also significantly reduced nitric oxide (NO) levels, which can be attributed to polyphenolic compounds inhibiting pro-inflammatory signalling pathways, such as NF-κB activation. Overall, this study emphasised the therapeutic potential of *A. melegueta* seeds and the influence of the structural composition of the bioactive compounds.

9.4. Miscellaneous Properties

Several other biological activities of *A. melegueta*, e.g., antidiabetic and hepatoprotective, are mediated through its antioxidative potential and anti-inflammatory property [59]. Anticancer activity of this plant was also reported. A recent study assessed the effect of *A. melegueta* seed extracts (standardized to 10% vanilloids, mainly 6-gingerol, 6-shogaol, and 6-paradol) on anxiety, stress, mood, and sleep using a randomized, double-blind, pilot clinical trial [1]. *In vitro* pharmacological assays targeting the endocannabinoid, serotonergic, and GABAergic systems were performed to elucidate the underlying mechanism of action. It was shown that *A. melegueta* extract could activate TRPV1 (noncanonical endocannabinoid receptor), modulate both hCB2R (canonical endocannabinoid receptor) and 5HT1AR (serotonin receptor), and inhibit FAAH (fatty-acid amide hydrolase enzyme), which is the enzyme primarily responsible for hydrolysing endogenous anandamide. After 48 h of intake, the extract significantly reduced anxiety and tension related to stress, improved overall mood, and enhanced sleep quality in participants at doses ranging from 50 to 150 mg, with no reported side effects.

10. Toxicity

Therapeutic applications of any plant extracts or their components not only depend on their pharmacological efficacy, but also on their toxicity profiles. When considering therapeutic uses of such materials, their toxicities must be considered to ensure that they have a good safety margin. Despite suggested potential therapeutic uses, comprehensive toxicological data on the extract of Grains of Paradise in animals are limited. To address this issue, a recent study evaluated the subchronic toxicity of Grains of Paradise extract in Sprague Dawley rats following 90 days of oral administration by gavage at doses of 0 (vehicle control), 135, 270, and 340 mg/kg bw/day, followed by a 28-day recovery period for the high-dose and control groups [60]. There was no mortality observed. Also,

there were no adverse clinical signs, or treatment-related differences in body weight, organ weights, and feed consumption were observed; haematology, clinical chemistry, and histopathology did not show any toxicologically significant changes. However, some statistically significant, non-dose-dependent alterations were detected, such as minor T3/T4 elevations at 340 mg/kg, but these lacked toxicological relevance without thyroid dysfunction. Considering all these data, the No Observed Adverse Effect Level (NOAEL) for Grains of Paradise extract was determined to be 270 mg/kg bw/day. Previously, chronic toxicity of *A. melegueta* was evaluated, but no significant toxicities could be detected [19]; no deaths or fur loss were observed in any of the animal groups. However, a slight but not significant decrease in body weight was noted in rats subjected to oral administration of 1 g/kg of both extracts. These results have demonstrated the long-term safety of Grains of Paradise, facilitating its potential therapeutic applications.

11. Conclusions

Grains of paradise (*A. melegueta*) possess therapeutic benefits and have long been used in traditional medicines to treat various ailments. Several studies, as outlined above, have demonstrated various pharmacological properties, including anti-inflammatory, anti-obesity, and antioxidant properties attributed to bioactive secondary metabolites, e.g., 6-gingerol, 6-shogaol, and 6-paradol, produced by this plant. Absence of any noticeable acute or chronic toxicities has made these pharmacological activities relevant to their therapeutic applications. While there are several *in vitro* and *in vivo* (using animal models) studies conducted with this plant and isolated compounds, there is still a pressing need for robust human clinical trials before this plant or its components can be applied in therapeutic interventions with full confidence. Additionally, key gaps in research on this plant include limited studies in different patient groups to extensively evaluate the pharmacokinetics, pharmacodynamics, bioavailability, and metabolic stability of bioactive compounds. Establishing standardised dosing remains a crucial challenge. Until these aspects are thoroughly explored, their direct application in modern clinical practice remains limited.

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