

(RESEARCH ARTICLE)



Bioactive component analysis of aqueous seed extract of *Aframomum melengueta*

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Abstract

Objective: *Aframomum melegueta* Schum (Zingiberaceae) is widely cultivated for its valuable seeds in the tropical region of Africa. This study identified the bioactive components present in aqueous seed extract of *Aframomum melengueta*

Methodology: Aqueous seed extract of *Aframomum melengueta* was qualitatively and quantitatively analyzed using Fourier-transform infrared spectroscopy (FTIR) and Gas chromatography coupled with flame ionization detector (GCFID).

Result: FTIR identified twelve organic functional groups of -OH, -NH₂, ≡CH, -NH₃⁺, -CH₃, -OH, -N=C=O, -C≡N, -C=C=C, -NH, -CH₃ and -1,3,5-trisubstituted benzenes. GCFID identified fifteen bioactive components namely kaemferol, naringenin, sapogernin, flavanones, anthocyanin, flavan-3-ol, cyanogenic glycoside, ribalinidine, rutin, catechin, resveratol, spartein, epicatechin, steroid and phytate.

Conclusion: The highest concentration of bioactive components was sapogernin 23.1038μg/ml, while the lowest concentration 1.0565μg/ml consisted of Naringenin.

Keywords: *Aframomum melengueta* (Alligator pepper); Bioactive components; Fourier-transform infrared spectroscopy (FTIR); Gas chromatography coupled with flame ionization detector (GCFID)

1. Introduction

Several plants exist with very high nutritive and medicinal values and yet remain unexploited for human and animal benefits. Plants are very vital because they are a fundamental part of life on earth, which generate the oxygen, food, fibers, fuel and medicine that allow humans and other higher life forms to exist. It is no small wonder then that green leaves are extremely beneficial to health (Nwala, Akaninwor & Monanu, 2013). Plants and their derivatives play key roles in world health and have long been known to possess biological activity (Omoboyowa, Nwodo & Joshua, 2013; Omoboyowa, Aja, Eluu & Ngobidi, 2017). Many of the indigenous medicinal plants are used as spices & food plants. They are also sometimes added to food meant for pregnant women and nursing mothers for medicinal purposes (Omale & Emmanuel, 2010).

Aframomum melengueta (Alligator pepper) (Zingiberaceae) is one of such plants having both medicinal and nutritive values, and popularly used as herbal remedy against a wide range of ailments, both in Nigeria and several other countries of the world (Nwozo and Oyinloye, 2011). *Aframomum melengueta* grows up to 1.5m in height, with purple

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flower that develop into long pod containing hundreds of small reddish brown aromatic and pungent seed (Onoja *et al.*, 2014; Magnifico & Tzemis, 2016). It's trumpet-shaped purple flowers develop into 5 to 7cm long pods containing numerous small reddish brown seeds which is a widely used spice in several parts of the world (Tropilab, 2008; Inegbenebor *et al.*, 2016). *Aframomum melegueta* is widely cultivated for its valuable seeds in the tropical region of Africa (Onoja *et al.*, 2014). The traditional indigenous names of the seed popularly known as alligator pepper in Nigeria are Ose-oji (Igbo), Atare (Yoruba), and Citta (Hausa) (Nosiri *et al.*, 2017; Onoja *et al.*, 2014; Nwozo and Oyinloye, 2011). Alligator pepper is a spice that is utilized in medicine due to its antioxidant and antimicrobial properties (Okibe *et al.*, 2020; Adegoke *et al.*, 2002). The spice from this pepper is used in West Africa for the purposes of alleviating stomach ache and diarrhea (Ilic *et al.*, 2010) as well as hypertension, tuberculosis and remedy for snake bites and scorpions (Ajaiyeoba *et al.*, 2006). The seeds are also used for culinary reasons due to the pungency of the seeds (Ilic *et al.*, 2010). They also tend to have general antimicrobial properties similar to many spices (Achinewu *et al.*, 1995) and helps in sexuality (enhances spermatogenesis) and aphrodisiac (Okibe *et al.*, 2020; Kamtchoung *et al.*, 2002).

This study is aimed at investigating the bioactive component analysis of aqueous seed extracts of *Aframomum melengueta*.

2. Methodology

2.1. Plants collection and preparation

The fruits of *Aframomum melegueta* were purchased from Relief Market, Owerri, Imo State, Nigeria. They were authenticated by a botanist, Mr. Francis Iwueze at the Department of Forestry and Wildlife, Federal University of Technology, Owerri (FUTO) and compared with existing collections deposited at the herbarium of the Department of Plant Science and Biotechnology, Michael Okpara University of Agriculture, Umudike with voucher specimen catalogue no. MOUAU/CVM/VPP/2013/03. The fruits were air dried at room temperature for two weeks. The outer coats of the seeds were removed, and the dried seeds put into an oven at a temperature of 50 °C for 4 hours then ground using electric blender to powder form and stored separately in an air tight container until required for extraction.

2.2. Extraction of *Aframomum melengueta* seed

Five hundred milligrams (500mg) of ground seeds were soaked in 500ml of distilled water for 48 hours and filtered with whatman filter paper No. 1. The filtrate was then evaporated in a water bath to concentrate the extract. The concentrate was dispensed into airtight sterile container and refrigerated at 4°C until required.

2.3. Percentage Yield

The extract obtained was weighed using an electronic weighing balance and the percentage yield calculated as follows:

$$\text{Percentage yield} = \frac{\text{weight of extract} \times 100}{\text{weight of starting material}}$$

2.4. Phytochemical analysis of *Aframomum melengueta*

The phytochemicals and functional units present in the aqueous seed extracts were analysed with the aid of gas chromatography with flame ionization detection (GC/FID) and *Fourier-transform infrared spectroscopy* (FTIR) respectively.

2.5. Fourier-transform infrared spectroscopy (FTIR)

This was determined by weighing 0.5g of the sample which was mixed with 0.5g of potassium bromide after which 1ml of nujol solvent was introduced into the sample with aid of a syringe to form a paste before introducing it into the instrument sample mold and allowed to scan at a wavelength of 600-4000 nm to obtain the sample's spectra wavelength.

2.6. Gas chromatography with flame ionization detector (GC/FID)

This was determined by weighing 0.2 g of the sample into a test tube to which 15ml of ethanol was added and allowed to react in a water bath at 60 °C for 60 mins. After the reaction time, the product was transferred to a separatory funnel, and separately washed with 20ml of ethanol, 10 ml of cold water, 10 ml of hot water and 3 ml of hexane. Extracts were then washed three times with 10 ml of 10 %v/v ethanol aqueous solution and dried with anhydrous sodium sulfate and the solvent was evaporated. The sample was solubilized in 1000 µl of petroleum ether of which 200 µl was transferred

to a vial for analysis. The analysis of phytochemicals was performed on a BUCK M910 gas chromatography equipped with HP-5MS column (30 m in length \times 250 μ m in diameter \times 0.25 μ m in thickness of film). Spectroscopic detection involved the use of an electron ionization system which utilized high energy electrons (70 eV). Pure helium gas (99.995%) was used as the carrier gas with flow rate of 1 mL/min. One microliter of the prepared 1% of the extract diluted with respective solvents was injected in splitless mode. Relative quantity of the chemical compounds present in each of the extracts was expressed as percentage based on peak area produced in the chromatogram.

3. Results

3.1. Functional groups of aqueous seed extracts of *Aframomum melengueta*

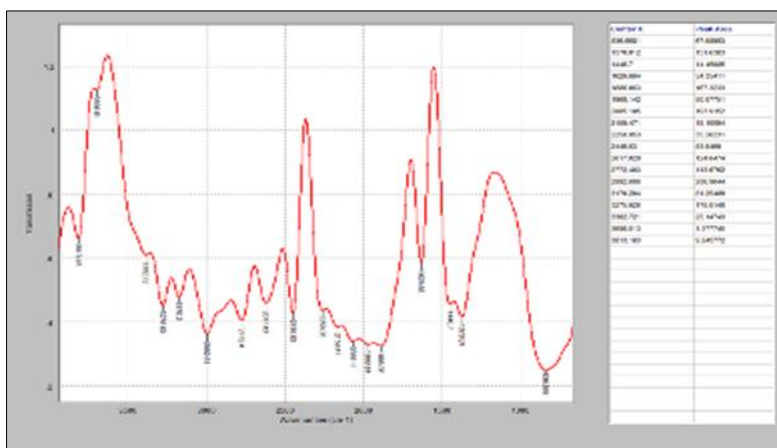


Figure 1 FTIR spectrum graph of aqueous seed extracts of *Aframomum melengueta*

Table 1 FTIR functional group of aqueous seed extract of *Aframomum melengueta*

Peak value	Bonds	Group and class
3696.513	OH stretch	-OH in alcohols and Phenols
3382.721	NH stretch	-NH ₂ in aromatic amines, primary amines and amides
3275.926	\equiv CH-H stretch	\equiv CH in acetylenes
3170.204	-NH ₃ ⁺ antisymmetric stretch	-NH ₃ ⁺ in amino acids
2772.403	CH stretching modes	-CH ₃ attached to O or N
2617.028	Associated OH stretching	-OH in phosphorus oxyacids
2258.953	N=C=O antisymmetric stretch	-N=C=O in isocyanates
2159.471	C \equiv N stretch	-C \equiv N in thiocyanates
1968.142	C=C=C stretch	-C=C=C in allenes
1629.664	NH deformation (amide ii band)	-NH in primary amides
1446.7	-CH ₃ antisymmetric deformation	-CH ₃ in aliphatic compounds
1370.012	CH ₃ symetric deformation	-CH ₃ in aliphatic compounds
836.568	CH out-of-plane deformation	-1,3,5-trisubst benzenes

Fourier-transform infrared spectroscopy identified important functional groups (Table 1) of organic compounds ranging from complex -OH in alcohols and phenols, -NH₂ in aromatic amines, primary amines and amides, \equiv CH in acetylenes, -NH₃⁺ in amino acids, -CH₃ attached to O or N, -OH in phosphorus oxyacids, -N=C=O in isocyanates, -C \equiv N in thiocyanates, -C=C=C in alkenes, -NH in primary amides, -CH₃ in aliphatic compounds, and -1,3,5-trisubstituted benzenes.

3.2. Identification of chemical constituents

Bioactive compounds extracted from different extracts were identified based on GC retention time on HP-5MS column and matching of the spectra with computer software data of standards (Replib and Mainlab data of GC–MS systems) (Figure 2).

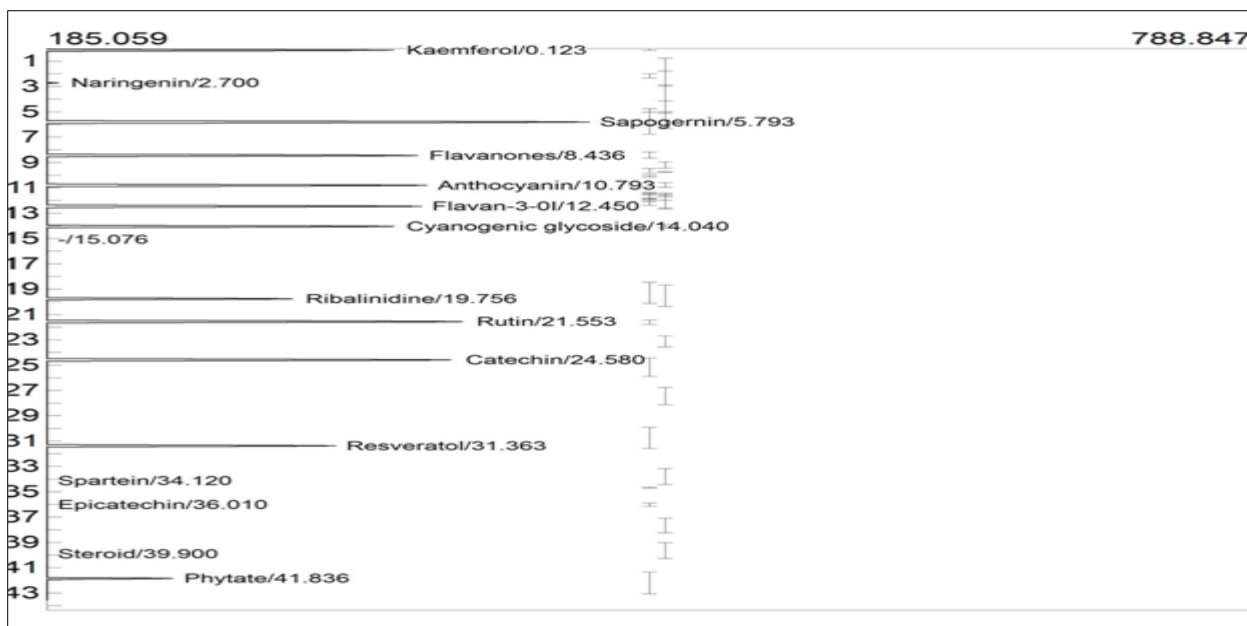


Figure 2 GCFID chromatogram of aqueous seed extracts of *Aframomum melengueta*

Bioactive compounds extracted from the seed were identified based on GC retention time on HP-5MS column and matching of the spectra with computer software data of standards (Replib and Mainlab data of GC–MS systems). The identified bioactive components according to retention time ranged from 1.06 $\mu\text{g}/\text{ml}$ to 23.10 $\mu\text{g}/\text{ml}$. The highest concentration of bioactive components was sapogernin 23.10 $\mu\text{g}/\text{ml}$ while the lowest concentration of 1.06 $\mu\text{g}/\text{ml}$ was for Naringenin (Table 2).

Table 2 GCFID phytochemical concentrations of aqueous seed extracts of *afmomum melengueta*

Component	Concentration ($\mu\text{g}/\text{ml}$)
Kaempferol	15.68
Naringenin	1.06
Sapogernin	23.10
Flavannones	18.41
Anthocyanins	13.45
Flavan-3-ol	11.09
Cyanogenic glycosides	12.64
Ribalinidine	10.13
Rutin	11.75
Catechinn	10.57
Resveratol	6.73
Sparte in	1.92
Epicatechin	1.23

Steroids	1.93
Phytates	6.73

4. Discussion

The results obtained from the phytochemical screening (Figure 2 and Table 2) revealed the presence of major classes of phytochemicals. The phytochemical and bioactive components of the aqueous seed extracts of *Aframomum melengueta* and their pharmacological benefits are elucidated.

ALKALOID: Alkaloids identified are sparteine and ribalinidine.

4.1. Sparteine

Sparteine is a quinolizidine alkaloid and a quinolizidine fundamental parent (NCBI, (2023)). Sparteine is a lupin alkaloid containing a tetracyclic bis-quinolizidine ring system derived from three C₅ chains of lysine, or more specifically, L-lysine (Dewick, 2009). The first intermediate in the biosynthesis is cadaverine, the decarboxylation product of lysine catalyzed by the enzyme lysine decarboxylase (LDC) (Golebiewski & Spenser, 1988). Sparteine is a plant alkaloid derived from *Cytisus scoparius* and *Lupinus mutabilis* which is thought to chelate the bivalent metals calcium and magnesium. It is a sodium channel blocker, so it falls in the category of class 1a antiarrhythmic agents (DrugBank, 2003). It has been used as an oxytocic and an anti-arrhythmia agent (DeVoe *et al.*, 1979). It has also been of interest as an indicator of CYP2D6 genotype (MeSH, 2023).

Sparteine sulphate administration increases plasma insulin and decreases plasma glucose and adrenaline in non-insulin dependent (Type II) diabetic subjects and also had evident hypoglycaemic effect in the presence of high plasma glucose level produced by biostator changing glucose infusion potentiated by simultaneous infusion of arginine (Paolisso *et al.*, 1988). Chronic myocarditis can be produced in rabbits by the repeated injection of spartein sulphate and epinephrin chloride. Strong and Gordon (1923) reported that a permanent enlargement followed repeated injections of these drugs. Sparteine is not currently FDA-approved for human use, and its salt, sparteine sulfate, is one of the products that have been withdrawn or removed from the market for reasons of safety or effectiveness (COFR, 2023).

4.2. Ribalinidine

Ribalinidine is a quinoline alkaloid compound with free radical scavenging activity (Nwiloh *et al.*, 2016; Onuah *et al.*, 2019). Ribalinidine possesses the molecular formula C₁₅H₁₇NO⁺ with one N-methyl and gem-C-dimethyl groups, two active hydrogens and no methoxyl group according to analytical, NMR and mass spectral data (Corral R.A. *et al.*, 1968).

Ribalinidine have been reported to play a beneficial role in visual acuity, treatment of cancer, heart disease, age-related neurodegenerative disorders and in angiogenesis. Ribalinidine have been reported to have free radical scavenging function (Rahmani & Sukari, 2010; Ugoeze *et al.*, 2020).

4.3. Polyphenols

Polyphenols are a large group of secondary metabolites extensively distributed in plant products, and have been implicated in improving human health by reducing chronic disease (Ishisaka *et al.*, 2013; Chen *et al.*, 2022). The basic mechanisms implicated in the potential health effects of polyphenols are mainly the inhibition of lipid and DNA oxidation (antioxidant activity) and the regulation of gene expression (Kris-etherton *et al.*, 2002; Patil *et al.*, 2009).

4.4. Flavonoid

In 1930, a new chemical substance isolated from oranges was discovered by Prof. Albert Szent Gyorgyi from University of Szeged, Hungary; it was believed to be a new member of the vitamin family and initially identified as vitamin P but later recognized as a flavonoid (Kwon *et al.*, 2004; Kim & YunChoi, 2008). The flavonoids are bioactive compounds belonging to the polyphenols, a group that can be found in all plants and known as secondary metabolites responsible for protecting plants against oxidizing agents such as ultraviolet rays, chemical compounds, and pollution (Calderón-Montañaño *et al.*, 2011; Silva dos *et al.*, 2021). More than 6,000 varieties of flavonoids have been identified and knowledge on their antioxidant action is well consolidated (Jäger & Saaby, 2011; Silva dos *et al.*, 2021). Several lines of evidence suggest that flavonoids that originated from vegetables and medicinal plants have beneficial effects on diabetes by improving glycemic control, lipid profile, and antioxidant status (Ghorbani, 2017). Moreover, since the 2000s, an increasing number of studies have highlighted many beneficial effects of flavonoids associated to their cardioprotective,

anticoagulant, antiplatelet, antibacterial, antiviral, antifungal, anti-inflammatory, antitumor, and antineuroinflammatory activity (Kwon *et al.*, 2004; Kim & Yun-Choi, 2008; Jeong *et al.*, 2009; Bai *et al.*, 2011; Pick *et al.*, 2011; Woo *et al.*, 2012; Tronina *et al.*, 2013; Lee *et al.*, 2013; Wang *et al.*, 2013; Choi *et al.*, 2014; Kimet *et al.*, 2014; Park *et al.*, 2014; Materska *et al.*, 2015; Silva dos *et al.*, 2021). From the investigation, flavonoids identified include: Flavan-3-ol, rutin, resveratrol, anthocyanin, flavanones, naringenin and kaempferol.

4.5. Flavan-3-ol

Dietary flavonoids are a structurally diverse set of naturally occurring polyphenolic compounds in plant-based foods, and flavan-3-ols are derivatives of flavanols, a major subclass of flavonoids, that include complex, bioactive monomeric and polymeric compounds found in tea leaves, cocoa, grapes, and other foods (Sesso *et al.*, 2022). Flavan-3-ols are a major class of dietary bioactives (Schroeter *et al.*, 2010; Lupton *et al.*, 2014; Ottaviani *et al.*, 2018), belonging to the group of polyphenolics, commonly found in tea, pome fruits, berries, cocoa-derived products and nuts. They are derivatives of flavans that possess a 2-phenyl-3, 4-dihydro-2H-chromen-3-ol skeleton. Flavan-3-ols are structurally diverse and include a range of compounds, such as catechin, epicatechin gallate, epigallocatechin gallate, proanthocyanidins, theaflavins, thearubigins. They play a part in plant defense and are present in the majority of plants (Ullah *et al.*, 2017). Flavan-3-ols are a sub-group of flavonoids, or healthy plant compounds found in many foods and drinks, such as tea, apples, berries, cocoa and red wine. Increasing attention has been given to this group of non-nutritive dietary compounds, bioactives, thought to exert physiological effect and to modulate disease risk (Ottaviani *et al.*, 2020). For decades, research has accumulated consistently demonstrating their ability to help reduce the risk of diet-related conditions such as heart disease, stroke and type-2 diabetes through a variety of mechanisms (Taylor, 2023).

High blood pressure is a leading disease risk factor globally, and cardiovascular disease (CVD) is a main cause of death (GBD, 2015). Accumulating evidence from dietary intervention studies shows that the intake of flavan-3-ols improves vascular function in healthy adults in intervention studies (Ried *et al.*, 2017). They are therefore of great interest for the development of dietary recommendation for the prevention of cardio-vascular diseases. Indeed, multiple clinical dietary intervention studies have demonstrated flavanol-intake related cardiovascular health benefits by assessing physiological endpoints including blood pressure, fowl-mediated arterial dilation, augmentation index, pulse wave velocity and arterial stiffness, as well as atherogenesis (Schroeter *et al.*, 2006; van Praag *et al.*, 2007; Sansone *et al.*, 2015; Ottaviani *et al.*, 2020). Research has shown that flavan-3-ols may affect vascular function, blood pressure, and blood lipids, with only minor effects demonstrated (Ried *et al.*, 2017; Raman *et al.*, 2019). They exert protective effects by helping to improve blood pressure, blood flow, cholesterol levels and even blood sugar, among others. Flavan-3-ols have even been shown to help protect the body's cells from damage as we age (Taylor, 2023). Food-based evidence indicates that intake of 400–600 mg per day of flavan-3-ols could have a small positive effect on cardiovascular biomarkers as well as diabetes (Crowe-White *et al.*, 2022; Taylor, 2023).

Flavan-3-ols have been reported to exhibit several health beneficial effects by acting as antioxidant, anticarcinogen, cardio-preventive, antimicrobial, anti-viral, and neuro-protective agents (Aron & Kennedy, 2008).

4.6. Rutin

Rutin is a flavonoid with a wide range of biological activities comprising quercetin and the disaccharide rutinose (rhamnose and glucose). Rutin is found in many plants (such as buckwheat seeds), fruits (such as citrus fruits), and vegetables (Tang *et al.*, 2011, Wu *et al.*, 2011; Wang *et al.*, 2012). Rutin is a glycone of quercetin with a flavonol structure (Xu *et al.*, 2014).

Rutin (quercetin-3-O-rutinoside) is a multifunctional natural flavonoid glycoside with profound effects on the various cellular functions under pathological conditions (Habtemariam, 2016). Rutin (Rutoside) shows a wide range of biological activities including anti-inflammatory, antidiabetic, antioxidant, neuroprotective, nephroprotective, hepatoprotective and reducing A β oligomer activities (Ghorbani, 2017). Rutin is a powerful phenolic antioxidant that has various pharmacological properties, including antitumor, anti-inflammatory, anti-diarrheal, anti-mutagenic, myocardial protecting, and immune-modulator. Several reports have demonstrated that rutin scavenges superoxide radicals, maintains the levels of biological antioxidants, increases antioxidant enzymatic activity *in vitro*, reduces lipid peroxidation and cytokine production, and prevents cognitive impairment following injuries, such as hypoxia/ischemia and CNS injuries in rat models. Previous studies showed that rutin could inhibit A β aggregation and cytotoxicity, attenuate oxidative stress, and decrease the production of nitric oxide and proinflammatory cytokines *in vitro* (Xu *et al.*, 2014).

Rutin is an important nutritional supplement because of its many pharmacological properties including anti-carcinogenic, cytoprotective, anti-platelet, anti-thrombotic, vasoprotective, and cardioprotective activities (Novakovic *et al.*, 2006). In addition, rutin is a powerful antioxidant and anti-inflammatory polyphenol (Chen *et al.*, 2000). Rutin and its analogues, such as epigallocatechin-3-gallate (EGCG) and quercetin, act as efficient radical inhibitors and are reported to rescue spatial memory impairment in rats with cerebral ischemia (Pu *et al.*, 2007; Wang *et al.*, 2012). The results of current experimental studies support the potential of rutin to prevent or treat pathologies associated with diabetes (Ghorbani, 2017).

Rutin attenuates vancomycin-induced renal tubular cell apoptosis via suppression of apoptosis, mitochondrial dysfunction, and oxidative stress (Xu *et al.*, 2014; Habtemariam, 2016; Ghorbani, 2017; Abdel-Aleem & Khaleel, 2018). Pretreatment with rutin in chronic dexamethasone-administered mice attenuated cognitive deficits and brain impairment (Tongjaroenbuangam *et al.*, 2011). Numerous investigations demonstrate that the analogues of rutin can interfere with A β aggregation and neurotoxicity, prevent oxidative stress induced by A β , reduce A β 42 levels in mutant human APP-overexpressing cells, and decrease senile plaques in the brain of APP transgenic mice (Rezai-Zadeh *et al.*, 2005; Ansari *et al.*, 2009; Lee *et al.*, 2009; Bieschke *et al.*, 2010; Dragicevic *et al.*, 2011; Pocernich *et al.*, 2011). These effects of rutin analogues suggest that they are promising agents for the treatment of AD (Wang *et al.*, 2012).

Due to the ability of rutin and/or its metabolites to cross the blood brain barrier, it has also been shown to modify the cognitive and various behavioral symptoms of neurodegenerative diseases. Among the most relevant mechanisms involved are effect on amyloid beta (A β) processing, aggregation and action; alteration of the oxidant-antioxidant balance associated with neuronal cell loss; removing the inflammatory component of neurodegeneration, etc. The effect resulting from its physicochemical features related to effects like metal chelation and bioavailability (Habtemariam, 2016).

Rutin, a polyphenol compound has been reported to inhibit A β aggregation and cytotoxicity, attenuates oxidative stress, and decreases the production of nitric oxide and pro-inflammatory cytokines *in vitro*. Orally administered rutin significantly attenuated memory deficits in AD transgenic mice, decreased oligomeric A β level, increased super oxide dismutase (SOD) activity and glutathione (GSH)/glutathione disulfide (GSSG) ratio, reduced GSSG and malondialdehyde (MDA) levels, down regulated microgliosis and astrocytosis, and decreased interleukin (IL)-1 β and IL-6 levels in the brain. These results indicated that rutin is a promising agent for AD treatment because of its antioxidant, anti-inflammatory, and reducing A β oligomer activities which are implicated in Alzheimer's disease (AD), a progressive, neurodegenerative disease characterized by extracellular β -amyloid (A β) plaques and intracellular neurofibrillary tangles in the brain. A β aggregation is closely associated with neurotoxicity, oxidative stress, and neuronal inflammation. The soluble A β oligomers are believed to be the most neurotoxic form among all forms of A β aggregates (Xu *et al.*, 2014).

Proposed mechanisms for the antihyperglycemic effect of rutin include a decrease of carbohydrates absorption from the small intestine, inhibition of tissue gluconeogenesis, an increase of tissue glucose uptake, stimulation of Insulin secretion from beta cells, and protecting Langerhans islet against degeneration. Rutin also decreases the formation of sorbitol, reactive oxygen species, advanced glycation end-product precursors, and inflammatory cytokines. These effects are considered to be responsible for the protective effect of rutin against hyperglycemia- and dyslipidemia-induced nephropathy, neuropathy, liver damage, and cardiovascular disorders (Ghorbani, 2016).

4.6.1. Epicatechin

Epicatechin is a type of flavonoid which is mainly found in *Spondias mombin* green tea (*Camellia sinensis*) and dark chocolate. Polyphenols constitute 30-40% of the extractable solids from the dried stem bark. The main catechins present are epicatechin, and epigallocatechin (Nakayam *et al.*, 1993; Aina *et al.*, 2017). The flavanol (-)-epicatechin is one of the most abundant flavonoids present in different fruits such as apples, blackberries, broad beans, cherries, grapes, pears, raspberries, cocoa, and tea leaves (Shukla *et al.*, 2019). (-)-epicatechin is the most abundant flavanol found in and absorbed from dark chocolate, and is thought to exhibit health-promoting biological activity (Ottaviani *et al.*, 2011; Schwarz *et al.*, 2018).

Epicatechin has been extensively researched for their diverse actions on human health and as therapeutic agents in the treatment of various human infections, especially resistant emerging and re-emerging infections (Aina *et al.*, 2017). However, (-)-epicatechin undergoes substantial metabolism into structurally related (-)-epicatechin metabolites before entering the circulation, which may or may not alter its function (Actis-Goretta *et al.*, 2012; Actis-Goretta *et al.*, 2013; Ottaviani *et al.*, 2016; Schwarz *et al.*, 2018).

Epicatechins have proven diverse benefits to human health, reducing the risks of diabetes mellitus and cardiovascular diseases. Their pharmacological effects are anti-hyperlipidaemic, anti-inflammatory, antioxidative, anticarcinogenic, and cytoprotective. These flavonoids can be used as therapeutic agents individually or in combination with other synthetic drugs and antibiotics to produce a new generation of phytopharmaceuticals (Aina *et al.*, 2017). Epicatechins are effective scavengers of free radicals such as reactive oxygen and nitrogen species and superoxide. In a study on the effect of *Spondias mombin* extract in intoxication of the liver, the extract scavenged free radicals and protected the liver from oxidative stress that would have brought about hepatic carcinogenesis (Huang *et al.*, 2006).

They are potent antioxidants, with antiviral, antimalarial and anticarcinogenic properties, among others. Frequent consumption of epicatechin has been proven to have health benefits (Aina *et al.*, 2017). In addition to its potential beneficial effects on endothelium and vascular function, (–)-epicatechin demonstrates antioxidant properties. In one study, an increase in plasma epicatechin was associated with an increase in plasma antioxidant capacity and a concomitant decrease in plasma oxidation products (Rein *et al.*, 2000). As a flavonoid with a complex structure, as well as being metabolized before entering the circulation, it is difficult to describe the exact mechanism of action through which (–)-epicatechin acts as an antioxidant. It is possible that (–)-epicatechin acts as an antioxidant both directly as a scavenger of free radicals and indirectly as a modulator of superoxide dismutase and glutathione peroxidase (Simos *et al.*, 2012; Schwarz *et al.*, 2018).

Many *in vitro* and *in vivo* studies in various tissues support the antiinflammatory effects of the (–)-epicatechin by attenuating the activation of the NF- κ B signaling pathway (Shukla *et al.*, 2019). Additionally, (–)-epicatechin was demonstrated to be the only catechin stereoisomer capable of inducing vasodilation of the femoral artery upon direct infusion into the bloodstream (Schwarz *et al.*, 2018). Scientists investigated whether epicatechin could down regulate the expressions of inducible nitric oxide synthase and cyclooxygenase-2 as well as the productions of NO, PGE₂, and pro inflammatory cytokines (IL-1 β , IL-6, and TNF- α) in LPS-induced RAW264.7 cells. It can be correlated with inhibition of activation of an inhibitor of κ B kinase α/β and sequential translocation of NF- κ B p50/P65 subunits (Shukla *et al.*, 2019).

Results from human trials indicate that (–)-epicatechin elicits beneficial effects on the vascular system (Schroeter *et al.*, 2006). Acute administration of 200 mg of (–)-epicatechin resulted in the augmentation of nitric oxide production and reduced endothelin-1, a marker of oxidative stress, in healthy men (Loke *et al.*, 2008). Similar results were reported for nitric oxide production in healthy males after ingestion of (–)-epicatechin-rich cocoa (Schroeter *et al.*, 2006; Schwarz *et al.*, 2018).

Epicatechin can improve several parameters of visceral fat inflammation in high-fat diet (HFD)-fed mice. Among them, epicatechin mitigated adipose macrophage infiltration (lower F4/80 and NOX2 protein levels), the activation of proinflammatory signals (NF- κ B), and tissue levels of cytokines (TNF α) and chemokines (MCP-1) (Shukla *et al.*, 2019). Epicatechin and other polyphenols decrease the susceptibility of low-density lipoprotein to oxidation, which prevents the initiation of atherosclerosis (Lavanchy, 2011). Attenuation of adipocyte endoplasmic reticulum and oxidative stress by epicatechin could contribute to decreased inflammation and improved visceral adipose tissue insulin sensitivity (Shukla *et al.*, 2019).

Pre-treatment with epicatechin prior to exposure of gamma radiation prevents hepatic and testicular damage which maybe due to oxidative stresses produced by the formation of free radicals as a result of radiation. Epicatechin is radioprotective, especially to patients undergoing radiotherapy (Lavanchy, 2011).

Epicatechins are neuroprotective because they block the neurotoxic effects of the HIV proteins that cause oxidative stress (Huang *et al.*, 2006). HIV proteins Tat and gp 120 are known to cause neurotoxicity in humans via mechanisms that activate macrophages and glial cells as well as oxidative stress (Aina *et al.*, 2017).

Epicatechin has also been demonstrated to modulate macronutrient metabolism in normal and overweight subjects (Gutiérrez-Salmeán *et al.*, 2014). Oral (–)-epicatechin supplementation at a dose of 1 mg/kg of bodyweight decreased the respiratory quotient after meal consumption, suggesting a higher rate of fat oxidation. In patients with type 2 diabetes and heart failure, 100 mg per day of (–)-epicatechin for 3 months increased peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1 α), silent mating type information regulation 2 homolog (SIRT1), and mitochondrial transcription factor A (Tfam) (Taub *et al.*, 2012). Consequently, mitochondrial structure was enhanced, although an increase in mitochondrial quantity was not observed. In another study, (–)-epicatechin administration reduced myostatin and increased markers of skeletal muscle myogenesis in both young and old mice (Gutiérrez-Salmeán *et al.*, 2014). Furthermore, in humans, ingestion of 1 mg/kg of bodyweight of (–)-epicatechin for 7 days increased bilateral grip strength by roughly 7% and demonstrated a favorable change in the follistatin-to-myostatin ratio (Gutiérrez-Salmeán *et al.*, 2014; Schwarz *et al.*, 2018).

Because of the aforementioned observations with (–)-epicatechin supplementation, it has been suggested that it may be useful as a means to increase exercise adaptations (Craig *et al.*, 2015). Fifteen days of (–)-epicatechin supplementation alone resulted in increased exercise performance, reduced muscle fatigue, increased muscle capillarity and increased mitochondrial biogenesis in mice (Schwarz *et al.*, 2018; Nogueira *et al.*, 2011). They exhibit a promising future as a drug formulation that is cost-effective, highly biocompatible, and with low toxicity (Brown & Arthur, 2001; Aina *et al.*, 2017).

4.7. Catechins

Catechins are polyphenolic compounds belonging to the flavanol subfamily of flavonoids. The most abundant dietary sources of catechins are green tea, cocoa products, and wine (Kopustinskiene *et al.*, 2021). Catechins are an important constituent of tea flavor and soup color (Bernatoniene & Kopustinskiene 2018). Catechin is a common flavanol found in a variety of foods and contains two stereogenic carbons and, thus, can exist as four distinct stereoisomers, despite each having the same chemical formula: (+)-catechin, (–)-catechin, (+)-epicatechin, and (–)-epicatechin (Ottaviani *et al.*, 2011; Schwarz *et al.*, 2018). Catechin compounds are the main functional components in tea, accounting for 12% to 35% of the dry weight of tea. The catechin compounds in tea tree mainly include epigallocatechin gallate (EGCG), epicatechin gallate (ECG), epigallocatechin (EGC), epicatechin (EC), gallocatechin gallate (GCG), catechin gallate (CG), gallocatechin (GC), and catechin (C) (Chen *et al.*, 2003; Chen *et al.*, 2022).

Various physiological activities of catechins have been fully confirmed in cell and animal models (Chen *et al.*, 2022). Catechins have been shown to possess beneficial effects in many pathological conditions including cardiovascular diseases which are currently one of the main causes of mortality in the world (Kopustinskiene *et al.*, 2021). The role of catechins in regulating cell homeostasis, in which they act as a free radical scavenger and metal ion chelator, their protective mechanism on mitochondria, and the protective effect of catechins on mitochondrial deoxyribonucleic acid (DNA), has been investigated. The catechin compounds which are rich in tea possess effective antioxidant activity, especially acetylated catechins such as epicatechin gallate (ECG) and epigallocatechin gallate (EGCG), and are able to protect mitochondria from reactive oxygen species. Catechins have effects on mitochondrial functional metabolic networks through regulation of mitochondrial function and biogenesis, improving insulin resistance, regulating intracellular calcium homeostasis, and regulating epigenetic processes (Chen *et al.*, 2022). Furthermore, catechins may regulate metabolic processes via direct effects on mitochondria, which are responsible for energy supply in the cells (Kopustinskiene *et al.*, 2021).

Due to their ability to donate electrons and hydrogen atoms, catechin compounds have shown various potential neuroprotective properties (Chen *et al.*, 2022). Catechins are potent antioxidants, although under pathological conditions they act as prooxidants, modulating signal transduction, inflammation, and cell death regulation pathways (Kopustinskiene *et al.*, 2021). Catechins are reactive oxygen species (ROS) scavengers and metal ion chelators, whereas their indirect antioxidant activities comprise induction of antioxidant enzymes, inhibition of pro-oxidant enzymes, and production of the phase II (Bernatoniene & Kopustinskiene 2018).

Catechins are metal ion chelators, and catechins can form stable complexes with various metal ions, such as Fe²⁺, Al³⁺, Ca²⁺, Cr³⁺, Mn²⁺, and Pb²⁺. It has been shown by large amount of evidence which indicates that transition metal ions, especially iron and copper ions, act as catalysts for the oxidative damage of biomolecules and are important factors causing oxidative stress (Chen *et al.*, 2022).

4.8. Resveratrol

Resveratrol is an antioxidant-like compound found in red wine, berries and peanuts (Gambini *et al.*, 2015; Weiskirchen & Weiskirchen, 2016). Resveratrol is a naturally occurring polyphenolic **fat-soluble** compound and antioxidant that is often described as a modern-day **fountain of youth**. Studies associated with this antioxidant are so compelling that it is becoming one of the most favourite supplements as it shows a real promise of manifold health benefits (WebMD 2005). The skins and seeds of grapes and berries contain resveratrol, making red wine high in this compound which helps lower cholesterol (Soleas *et al.*, 1997; Gambini *et al.*, 2015; Jennings, 2023).

Resveratrol supplements have been linked to many exciting health benefits, including protecting brain function and lowering blood pressure (Liu *et al.*, 2015; Braidy *et al.*, 2016; Kuršvietienė *et al.*, 2016; Moussa *et al.*, 2017). Systolic blood pressure typically goes up with age, as arteries stiffen and when high, it's a risk factor for heart disease. Resveratrol supplements are used to lower blood pressure by increasing the production of nitric oxide (López-Sepúlveda *et al.*, 2008; Xia *et al.*, 2014; Liu *et al.*, 2015; Bonnefont-Rousselot, 2016; Jennings, 2023).

Resveratrol might have many effects in the body, including expanding blood vessels and reducing blood clotting thus increasing the risk in people with bleeding disorders (WebMD 2005). High doses has been shown to stop blood from clotting in test tubes, it's possible it could increase bleeding or bruising when taken with anti-clotting drugs, such as heparin or warfarin, or some pain relievers (Pace-Asciak *et al.*, 1995; Bertelli *et al.*, 1995; Chow *et al.*, 2010; Jennings, 2023). Resveratrol might increase the risk of bleeding during and after surgery and should be discontinued at least 2 weeks before a scheduled surgery (WebMD 2005).

4.9. Resveratrol is most commonly used for high cholesterol, cancer, heart disease, and many other conditions (WebMD 2005)

Researchers reported that the average total cholesterol levels and body weight of mice decreased, and their levels of “good” HDL cholesterol increased by reducing the effect of an enzyme that controls cholesterol production (Xie *et al.*, 2013; Mendes *et al.*, 2016; Jennings, 2023). Taking resveratrol by mouth increased weight loss in overweight and obese adults (WebMD 2005).

There is evidence that resveratrol activates certain genes that ward off the diseases of aging (Hubbard *et al.*, 2013). Resveratrol supplements have lengthened lifespan in animal studies (Lam *et al.*, 2013; Wood *et al.*, 2014; Pallauf *et al.*, 2016). Resveratrol may set off a chain of events that protects brain cells from damage (Granzotto & Zatta, 2014). It seems to interfere with protein fragments called beta-amyloids, which are crucial to forming the plaques that are a hallmark of Alzheimer’s disease (Granzotto & Zatta, 2014; Regitz *et al.*, 2016; Jennings, 2023).

It may also decrease pain and swelling, reduce levels of sugar in the blood, and help the body fight against disease (WebMD 2005). Resveratrol has helped mice develop better insulin sensitivity and fight complications of diabetes. These benefits include increasing insulin sensitivity and preventing complications from diabetes (Sharma *et al.*, 2006; Fröjdö *et al.*, 2008; Chang *et al.*, 2011; Vallianou *et al.*, 2013; Jennings, 2023). Resveratrol may help relieve joint pain by preventing cartilage from breaking down (Elmali *et al.*, 2007; Csaki *et al.*, 2008; Mobasheri *et al.*, 2012; Jennings, 2023). It may be helpful for hay fever and weight loss (WebMD 2005).

Resveratrol is likely safe when used in amounts found in some foods. However, during pregnancy and breast-feeding, the source of resveratrol is important due to some negative effects (WebMD 2005). While resveratrol supplements are likely safe for most people, they could interact with certain medications (Bertelli *et al.*, 1995; Jennings, 2023). Resveratrol should be minimized in hormone-sensitive condition such as breast cancer, uterine cancer, ovarian cancer, endometriosis, or uterine fibroids as Resveratrol might act like estrogen thereby worsening the condition (WebMD 2005). However, resveratrol has shown exciting cancer-blocking activity in test tubes and animal studies by changing the gene expression in cancer cells to inhibit their growth and may interfere with the way certain hormones are expressed thus keeping hormone-dependent cancers from spreading (Tessitore *et al.*, 2000; Wang *et al.*, 2008; Zulueta *et al.*, 2015; Jennings, 2023).

4.10. Anthocyanins

Anthocyanins (ACNs) are natural bioactive water-soluble phenolic compounds, which represent one of the principal families of natural pigments (orange, red, violet, and blue colors) (Riaz *et al.*, 2016). More than 700 ACNs have been identified in nature, and they are produced by plants to attract insects to flowers for pollination and herbivorous animals to fruits for seed dissemination, as well as for the protection of plant cells against UV radiation damage (Markakis, 2012; Wallace & Giusti, 2013; Warner, 2015). These colored pigments appear red in acidic condition and show a blue hue in alkaline solution (Khoo *et al.*, 2017).

Anthocyanins are blue, red, or purple pigments found in plants. Anthocyanins colored pigments extracted from flowers, fruits, tubers and vegetables are traditionally used as dye and food colorant (Khoo *et al.*, 2017). ACNs are used in the food industry to replace synthetic colorants (Salehi *et al.*, 2014; Mazza & Miniati, 2018).

Besides being used as natural colorants, some of the anthocyanin-rich flowers and fruits have been traditionally used as medicine to treat various diseases as the value-added colorants that can be used for preventing several diseases, including CVDs, cancers, diabetes, some metabolic diseases, and microbial infection. Anthocyanins are plants pigments that possess several health benefits (Khoo *et al.*, 2017). Anthocyanins are well-known to have potent antioxidant and antiinflammatory activity, which explains the various biological effects reported for these substances suggesting their antidiabetic and anticancer activities, and their role in cardiovascular and neuroprotective prevention. ACNs are natural bioactive compounds with many pharmacological effects: antioxidant, antiinflammatory, prevention of age-related chronic diseases: cardiovascular disease (CVD), cancers, neurodegenerative, and eye-related diseases (Salehi *et al.*, 2014). Anthocyanins possess antidiabetic, anticancer, anti-inflammatory, antimicrobial, and anti-obesity effects, as well

as prevention of cardiovascular diseases (CVDs) (He *et al.*, 2011). ACNs also have antiviral properties as in vitro studies have shown that they can inhibit the replication of viruses such as herpes simplex, parainfluenza virus, syncytial virus, HIV, rotavirus, and adenovirus (Pour *et al.*, 2019). Anthocyanins also improve visual ability and have neuroprotective effect. Several mechanisms of action are reported for the anthocyanins in prevention of these diseases. In a nutshell, free-radical scavenging, changes in blood biomarkers, COX and MAPKs pathways, as well as inflammatory cytokines signaling are the typical mechanisms of action of these colored pigments in prevention of diseases. Therefore, anthocyanins extracted from edible plants are potential pharmaceutical ingredients (Khoo *et al.*, 2017).

4.11. Flavanones

A few decades ago, flavanones were considered as only minor flavonoids (Bohm, 1994), like chalcones, dihydrochalcones, dihydroflavonols and aurones. However, currently, the total number of known flavanones has increased to the point that they are now considered a major flavonoid class like flavones, isoflavones, flavanols, flavonols and anthocyanidins (Veitch & Grayer, 2006). Up to now about 350 flavanone aglycones and 100 flavanone glycosides have been identified in nature (Iwashina, 2000; Khan *et al.*, 2014). The flavanones, a type of flavonoids, are various aromatic, colorless ketones derived from flavone that often occur in plants as glycosides (Webster, 2014; Merriam-Webster, 2017). Flavones differ from flavanones by a C2–C3 double bond (Marais *et al.*, 2006). The flavanone class encompasses a wide array of compounds with O- and/or C-substitutions at the A- or B-ring, e.g., hydroxy, methoxy, methylenedioxy, O- and C-glycosyl, C-methyl, C-benzyl, C-hydroxymethyl, C-formyl, C-isoprenyl substituents (including furano or dihydrofurano rings), conjugations to stilbene, anastatin, phenolic acid, and diarylheptanoid moieties (Veitch & Grayer, 2008; Khan *et al.*, 2014). Flavanones may be regarded as the cornerstone of flavonoid biosynthesis as they are the precursors of all other flavonoid classes (Schijlen *et al.*, 2004; Martens & Mithofer, 2005). Moreover, in Citrus species, UDP-glucose flavanone-7-O-glucosyltransferase (UFGT) and UDP-rhamnose flavanone glucoside rhamnosyltransferase (UFGRT) sequentially convert the flavanone aglycones into their 7-O-b-D-glucosides and rhamnoglucosides (Lewinsohn *et al.*, 1989). Naturally occurring flavanones display the (S) configuration at C2 (Tomas-Barberan & Clifford, 2000) as a consequence of the enantioselectivity of the chalcone isomerase (CHI)-catalyzed intramolecular Michael addition within the chalcone precursor (Jez & Noel, 2002; Khan *et al.*, 2014). Flavanones are widely distributed in about 42 higher plant families especially in Compositae, Leguminosae and Rutaceae (Iwashina, 2000). Depending on the plant type, flavanones can be found in all plant parts, above and below ground, from vegetative part to generative organs: stem, branches, bark, flowers, leaves, roots, rhizomes, seeds, fruits, peels etc. The highest concentrations of flavanones are found in the peel as compared to the fleshy part of Citrus fruit (Nogata *et al.*, 2006). Orange juice is one of the most commonly consumed juices throughout the world and is a rich source of flavanones, particularly hesperidin and naringin. As one of the most readily absorbed flavonoid subclasses, flavanones have been shown to cross the blood-brain barrier (Gardener *et al.*, 2021). Flavanones are generally glycosylated by a disaccharide at position 7 (either a neohesperidose, which imparts a bitter taste, or a rutinose, which is flavorless) (Herrero *et al.*, 2012).

Major flavanones in plant species include hesperetin, naringenin, eriodictyol, isosakuranetin and their respective glycosides. Hesperetin and its derivatives are characteristic flavanones of sweet orange, tangelo, lemon and lime, while naringenin and its derivatives are those of grapefruit and sour orange (Khan *et al.*, 2014). Flavanones, including hesperidin and naringin, are polyphenolic compounds highly and almost exclusively present in citrus (Chanet *et al.*, 2012). These potentially bioactive compounds include phytoestrogens, carotenoids, ascorbic acid, citrus limonoids, organosulfur compounds and a good number of polyphenols (Kris-etherton *et al.*, 2002; Patil *et al.*, 2009).

Flavanones are known for their anti-inflammatory properties and may also help manage weight and cholesterol (Watson, 2019). Epidemiological studies reported an inverse relationship between their intake and the risk of cardiovascular diseases. Clinical and experimental data further showed their antihypertensive, lipid-lowering, insulin-sensitizing, antioxidative, and anti-inflammatory properties, which could explain their antiatherogenic action in animal models (Chanet *et al.*, 2012).

4.12. Naringenin

Naringenin is a flavonoid belonging to flavanones subclass. It is widely distributed in several Citrus fruits, bergamot, tomatoes and other fruits, being also found in its glycosides form (mainly naringin). Naringenin is one of the most important naturally-occurring flavonoid, predominantly found in some edible fruits, like Citrus species and tomatoes (Jadeja & Devkar, 2014; Mbaveng *et al.*, 2014; Zobeiri *et al.*, 2018) and figs belonging to smyrna-type *Ficus carica* (Soltana *et al.*, 2018). Chemically named as 2,3-dihydro-5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one, naringenin shows a molecular weight of 272.26 (C₁₅H₁₂O₅) (Salehi *et al.*, 2019).

Several biological activities have been ascribed to this phytochemical, among them antioxidant, antitumor, antiviral, antibacterial, anti-inflammatory, antiadipogenic and cardioprotective effects. Nonetheless, most of the data reported have been obtained from *in vitro* or *in vivo* studies (Salehi *et al.*, 2019). Growing evidence from both *in vitro* and *in vivo* animal studies have reinforced various naringenin pharmacological effects, including as hepatoprotective, anti-atherogenic, anti-inflammatory, anti-mutagenic, anticancer, antimicrobial agent, even suggesting its application in cardiovascular, gastrointestinal, neurological, metabolic, rheumatological, infectious and malignant diseases control and management (Pinho-Ribeiro *et al.*, 2016; Ke *et al.*, 2017; Karim *et al.*, 2018; Yin *et al.*, 2018; Salehi *et al.*, 2019).

Naringenin is endowed with broad biological effects on human health, which includes decrease in lipid peroxidation biomarkers and protein carbonylation, promotes carbohydrate metabolism, increases antioxidant defenses, scavenges reactive oxygen species, modulates immune system activity, and also exerts anti-atherogenic and anti-inflammatory effects (Wang *et al.*, 2015; NCBI 2018).

It has also been reported to have a great ability to modulate signaling pathways related to fatty acids metabolism, which favors fatty acids oxidation, impairs lipid accumulation in liver and thereby preventing fatty liver (Zobeiri *et al.*, 2018), besides efficiently impairing plasma lipids and lipoproteins accumulation (Jayachitra & Nalini, 2012). In addition, naringenin potentiates intracellular signaling responses to low insulin doses by sensitizing hepatocytes to insulin, besides being able to traverse the blood–brain barrier and to exert diverse neuronal effects, through its ability to interact with protein kinase C signaling pathways (Wang *et al.*, 2015).

Moreover, naringin was also shown to up-regulate gene expression of superoxide dismutase, catalase and glutathione peroxidase thereby contributing to fighting oxidative stress (Jeon *et al.*, 2001; Khan *et al.*, 2014).

Beneficial effects of naringenin on cis-platin-induced nephrotoxicity (Badarya *et al.*, 2005) were reported. Knekt *et al.* (2002) found an association between a high intake of hesperetin and naringenin and a lower incidence of cerebrovascular disease and asthma. The findings support the clinical importance of monoamine oxidase (MAO-A and B) inhibitors in the treatment of several neurological and psychiatric disorders. Among the several flavonoids (flavones, thioflavones and flavanones) tested the most active were the flavanones with highest selective inhibitory activity against MAO-B (Chimenti *et al.*, 2010).

The major citrus flavanones can be effective in fighting carcinogenesis by minimizing DNA damage, tumor development and proliferation. The pharmacological importance of flavanones can also be evaluated by their action against tumor development. Among flavanones, the naringenin and hesperetin aglycones and their glycosides are of particular interest because of their high prevalence in foods (Khan *et al.*, 2014). So *et al.* (1996) studied the effect of hesperetin and naringenin on the development of breast cancer induced by 7, 12-dimethylbenz[a]anthracene in female rats. The results showed that tumor development was delayed in rats fed with an orange juice/naringin-supplemented diet. Later on, concerning the anti-angiogenic effect of flavanones, an enzyme-linked immunosorbent assay (ELISA) was used to measure the vascular endothelial growth factor (VEGF) release from mammary adenocarcinoma human breast cancer cells. Naringin appeared more potent than rutin, apigenin, kaempferol and chrysin (Schindler & Mentlein, 2006). 8-Prenylnaringenin, a derivative of naringenin, inhibits angiogenesis induced by basic fibroblast growth factor (VEGF) or the synergistic effect of two cytokines in combination, in an *in vitro* and *in vivo* study (Pepper *et al.*, 2004; Khan *et al.*, 2014). The anti-cancer, anti-proliferative and anticarcinogenic effects have also been ascribed to this metabolite (Erlund *et al.*, 2021), mostly linked to its ability to repair DNA. In fact, cells exposition to 80 mM/L naringenin, during 24 h, led to 24% DNA hydroxyl damages reduction (NCBI, 2018).

Flavanones can protect DNA damage by their capacity to absorb UV light (Khan *et al.*, 2014). The results from a UV irradiated model of plasmidic DNA showed a considerable protecting effect of naringenin against UV-induced damage of DNA (Kootstra, 1994). The moderate antioxidant capacity of flavanones can also be useful in protecting against mutation by free radicals generated near DNA. Furthermore, naringin also inhibits H₂O₂-induced cytotoxicity and apoptosis, possibly via its effect on the H₂O₂-induced expression of an apoptosis-associated gene (Kanno *et al.*, 2003). Naringenin may exhibit anti-mutagenic changes by stimulating DNA repair, following oxidative damage in human prostate cancer cells (Gao *et al.*, 2006; Khan *et al.*, 2014).

Moreover, antiviral effects have been reported. Naringenin shows a dose-dependent inhibitory effect against dengue virus (Frabasil *et al.*, 2017), prevents intracellular replication of chikungunya virus (Ahmadi *et al.*, 2016), and inhibits assembly and long-term production of infectious hepatitis C virus particles in a dose-dependent manner (Wang *et al.*, 2015).

Unfortunately, this bioflavonoid is poorly absorbed by oral ingestion, with only 15% of ingested naringenin absorbed in the human gastrointestinal tract (NCBI 2018; Salehi *et al.*, 2019).

4.13. Kaempferol

Kaempferol (3,4',5,7-tetrahydroxyflavone) is a natural flavonol, a type of flavonoid, found in a variety of plants and plant-derived foods including kale, beans, tea, spinach, and broccoli (Holland *et al.*, 2022). It is slightly soluble in water and highly soluble in hot ethanol, ethers, and DMSO. Kaempferol is named for 17th-century German naturalist Engelbert Kaempfer (Merriam-Webster, 2023). Kaempferol is a secondary metabolite found in many plants, plant-derived foods, and traditional medicines (Calderón-Montaña *et al.*, 2012). Its flavor is considered bitter. Kaempferol (KPF) (C₁₅H₁₀O) is a flavonoid antioxidant found in fruits and vegetables.

Many studies have described the beneficial effects of dietary KPF in reducing the risk of chronic diseases, especially cancer and its derivatives in neurological diseases such as Alzheimer's disease, parkinson, ischemia stroke, epilepsy, major depressive disorder, anxiety disorders, neuropathic pain, and glioblastoma (Silva dos *et al.*, 2021).

KPF has presented a multipotential neuroprotective action through the modulation of several proinflammatory signaling pathways such as the nuclear factor kappa B (NF-κB), p38 mitogen-activated protein kinases (p38MAPK), serine/threonine kinase (AKT), and β-catenin cascade. In addition, there are different biological benefits and pharmacokinetic behaviors between KPF aglycone and its glycosides (Silva dos *et al.*, 2021). KPF promotes a protective effect on the brain, inhibiting proinflammatory cytotoxicity and the activity of important inflammatory pathways as NF-κB, p38MAPK, and AKT, resulting in an overall antiinflammatory and antioxidant action. It is suggested that KPF and some glycosylated derivatives (KPF-3-O-rhamnoside, KPF-3-O-glucoside, KPF-7-O-rutinoside, and KPF-4'-methyl ether) which have multipotential neuroprotective actions in the CNS diseases (Salehi *et al.*, 2019).

The antioxidant nature of KPF was observed in neurological diseases through MMP2, MMP3, and MMP9 metalloproteinase inhibition; reactive oxygen species generation inhibition; endogenous antioxidants modulation as superoxide dismutase and glutathione; formation and aggregation of beta-amyloid (β-A) protein inhibition; and brain protective action through the modulation of brain-derived neurotrophic factor (BDNF), important for neural plasticity. In conclusion, we suggest that KPF and some glycosylated derivatives (KPF-3-Orhamnoside, KPF-3-O-glucoside, KPF-7-O-rutinoside, and KPF-4'-methyl ether) have a multipotential neuroprotective action in CNS diseases (Silva dos *et al.*, 2021).

Among the various pharmacological effects presented by KPF, the anti-inflammatory action is the most striking, attributed mainly to its ability to inhibit the enzymes phospholipase A2, lipoxygenase, cyclooxygenase, and nitric oxide through the modulation of the enzyme nitric oxide synthase (iNOS) (Kim *et al.*, 2004; Yoon & Baek, 2005; Santangelo *et al.*, 2007). In addition, a previous *in vivo* study has proved the ability of KPF to overcome the blood-brain barrier (BBB) with a single dose of 600mg/kilograms (kg) in rats (Rangel-Ordóñez *et al.*, 2010; Salehi *et al.*, 2019).

4.14. Steroids

Steroid, are any of a class of natural or synthetic organic compounds characterized by a molecular structure of 17 carbon atoms arranged in four rings. Steroids are important in biology, chemistry, and medicine (Clayton & Kluger, 2023). Steroids (named after the steroid cholesterol (Harper, 2013) which was first described in gall stones from Ancient Greek *chole*- 'bile' and *stereos* 'solid' (Chevreul, 1815; Arago & Gay-Lussac, 1816) are biologically active organic compounds with four fused rings arranged in a specific molecular configuration. Steroids vary from one another in the nature of attached groups, the position of the groups, and the configuration of the steroid nucleus (or gonane).

Small modifications in the molecular structures of steroids can produce remarkable differences in their biological activities (Clayton & Kluger, 2023). Steroids can also be radically modified by changes to the ring structure for example; cutting ring B produces secosteroids one of which is vitamin D₃. Examples include anabolic steroids, the lipid cholesterol, the sex hormones estradiol and testosterone (Lednicer, 2011) and the anti-inflammatory corticosteroid drug dexamethasone (Rhen & Cidlowski, 2005).

The steroid group includes all the sex hormones, adrenal cortical hormones, bile acids, and sterols of vertebrates, as well as the molting hormones of insects and many other physiologically active substances of animals and plants (Clayton & Kluger, 2023).

Steroids have two principal biological functions, namely as important components of cell membranes that alter membrane fluidity; and as signaling molecules. Hundreds of steroids are found in plants, animals and fungi (IUBMB, 2011). Steroids such as cholesterol decrease membrane fluidity (Sadava *et al.*, 2011). Similar to lipids, steroids are highly concentrated energy stores. However, they are not typically sources of energy; in mammals, they are normally metabolized and excreted. All steroids are manufactured in cells from the sterols lanosterol (opisthokonts) or cycloartenol (plants). Lanosterol and cycloartenol are derived from the cyclization of the triterpene squalene (IUBMB, 2011).

Different categories of steroids are frequently distinguished from each other by names that relate to their biological source e.g., phytosterols (found in plants), adrenal steroids, and bile acids or to some important physiological function e.g., progesterones (promoting gestation), androgens (favouring development of masculine characteristics) and cardiotoxic steroids (facilitating proper heart function) (Clayton & Kluger, 2023). The major classes of steroid hormones, with prominent members and examples of related functions are (i) corticosteroids, cortisol, glucocorticoid whose functions include immunosuppression (ii) Mineralocorticoids, Aldosterone, a mineralocorticoid that helps regulate blood pressure through water and electrolyte balance (iii) Sex steroids: Progestogens, Progesterone, which regulates cyclical changes in the endometrium of the uterus and maintains a pregnancy (iv) Androgens: Testosterone, which contributes to the development and maintenance of male secondary sex characteristics (v) Estrogens, Estradiol, which contributes to the development and maintenance of female secondary sex characteristics (vi) Neurosteroids such as DHEA and allopregnanolone, Bile acids such as taurocholic acid, (vii) Aminosteroid neuromuscular blocking agents (mainly synthetic) such as pancuronium bromide, (viii) Steroidal antiandrogens (mainly synthetic) such as cyproterone acetate, (ix) Steroidogenesis inhibitors (mainly exogenous) such as alfatradiol, (x) Membrane sterols such as cholesterol, ergosterol and various phytosterols (xi) Toxins such as steroidal saponins and cardenolides/cardiac glycosides as well as the following class of (xii) Secosteroids (open-ring steroids): Vitamin D forms such as ergocalciferol, cholecalciferol and calcitriol.

Research has shown that steroids are active in affecting gene expression, translation, and enzyme activity (Rhen & Cidlowski, 2005). In short, they bring about their physiologic effects through a multitude of biochemical pathways. One such pathway is through their induction of the production of proteins called lipocortins. Glucocorticoids stem the production of inflammatory mediators such as leukotrienes and prostaglandins and effectively halt the inflammatory cascade (Ericson-Neilsen & Kaye, 2014).

As their wide-ranging side effects indicate, glucocorticoids can impact many systems throughout the body. Through negative feedback regulation of the hypothalamic-pituitary-adrenal (HPA) axis, exogenous glucocorticoids can directly induce hypopituitarism (Addison disease). Their actions on glucose metabolism can increase insulin resistance in tissues and increase fasting glucose levels. Glucocorticoids can act directly on osteoclasts to affect bone reabsorption and decrease calcium absorption in the gastrointestinal tract, resulting in osteopenia and osteoporosis (Stewart & Krone, 2011; Ericson-Neilsen & Kaye, 2014).

Mineralocorticoids, endogenously represented by aldosterone and deoxycorticosterone, effect physiologic changes by altering electrolyte (sodium and potassium) levels, causing volume changes to occur. Rather than being moderated by the HPA axis as glucocorticoid production is, mineralocorticoid production is mainly regulated by the renin-angiotensin-aldosterone system, although adrenocorticotropic hormone, a product of the HPA axis, does have minimal activity in stimulating aldosterone release (Stewart & Krone, 2011; Ericson-Neilsen & Kaye, 2014).

Steroids and their metabolites often function as signalling molecules (the most notable examples are steroid hormones), and steroids and phospholipids are components of cell membranes (Silverthorn *et al.*, 2016). Steroids play critical roles in a number of disorders, including malignancies like prostate cancer, where steroid production inside and outside the tumour promotes cancer cell aggressiveness (Lubik *et al.*, 2016). Among the synthetic steroids of therapeutic value are a large number of anti-inflammatory agents, anabolic (growth-stimulating) agents, and oral contraceptives (Clayton & Kluger, 2023). The antiinflammatory properties of steroids have been attributed to their inhibitory effects on the action of phospholipase A2, an enzyme critical to the production of inflammatory compounds (Ericson-Neilsen & Kaye, 2014).

4.14.1. Sapogernin

Sapogernin has anti-inflammatory and anticancer activities (Okonkwo-Uzor *et al.*, 2022, Jesus *et al.*, 2016).

4.14.2. Phytate

Phytate (myo-inositol hexaphosphate) is found in varieties of foods such as nuts, seeds and whole grains. They are also found in substantial amounts in roots and tubers (Ugoeze *et al.*, 2020).

Phytate inhibits kidney stone formation by complexing with calcium and preventing crystallization. Younger women (NHS II) with higher phytate intake had a lower risk of kidney stones compared to those with lower phytate intake (Dahl & Goldfarb, 2022; Grieff & Bushinsky, 2022). It is held that phosphorylated inositol, particularly phytic acid have parts in the secretion of insulin by the beta cells of the pancreas. Phytic acid has also been proposed to obstruct the beginning of plaque development and lower serum cholesterol and triglycerides (Urbano *et al.*, 2000; Schlemmer *et al.*, 2009; Gibson *et al.*, 2010; Ugoeze *et al.*, 2020).

Phytates and oxalates are some of the well-known anti-nutrients (Ugoeze *et al.*, 2020). While nutrients are associated with beneficial effects in human health, anti-nutrients, on the other hand, interfere with the absorption of minerals and hence are thought of as not so beneficial, though, some have valued health benefits. Their interference with nutrient absorption has been known to cause headaches, rashes, nausea, bloating and nutritional deficiencies (Popova & Mihaylova, 2019). While some anti-nutrients will bind to essential micronutrients to prevent the body from absorbing them, others may inhibit the optimal functioning of digestive enzymes, hence preventing the proper break down of food. Anti-nutrients are mostly of organic or synthetic structure and are highly reactive, hence capable of toxic effects (Ugoeze *et al.*, 2020).

4.15. Cyanogenic Glycosides (CNGlcs)

Cyanogenic glycosides (CNGlcs) are bioactive natural products (also called specialized plant products or secondary metabolites) derived from amino acids with oximes and cyanohydrins (α -hydroxynitriles) as key intermediates (Morant *et al.*, 2008). Structurally, these specialized plant compounds are characterized as α -hydroxynitriles (cyanohydrins) that are stabilized by glucosylation (Gleadow & Møller, 2014). Glucosylation of the labile cyanohydrin results in the formation of a CNGlc. CNGlcs are stable compounds, but when the β -glycosidic linkage is hydrolyzed through the action of a β -glycosidase, the labile cyanohydrin that is formed dissociates to release HCN in a process known as cyanogenesis (Morant *et al.*, 2008).

Cyanogenesis the release of toxic hydrogen cyanide from endogenous CNGlcs--is an effective defense against generalist herbivores but less effective against fungal pathogens. In the course of evolution, CNGlcs have acquired additional roles to improve plant plasticity, i.e., establishment, robustness, and viability in response to environmental challenges. CNGlc concentration is usually higher in young plants, when nitrogen is in ready supply, or when growth is constrained by nonoptimal growth conditions (Gleadow & Møller, 2014).

Cyanogenic glycosides are natural plant toxins that are present in several plants, most of which are consumed by humans (Bolarinwa *et al.*, 2016). Efforts are under way to engineer CNGlcs into some crops as a pest control measure, whereas in other crops efforts are directed toward their removal to improve food safety (Gleadow & Møller, 2014). Cyanide is formed following the hydrolysis of cyanogenic glycosides that occur during crushing of the edible plant material either during consumption or during processing of the food crop. Exposure to cyanide from unintentional or intentional consumption of cyanogenic glycosides may lead to acute intoxications, characterized by growth retardation and neurological symptoms resulting from tissue damage in the central nervous system (CNS). Processing methods can detoxify cyanogenic glycosides and reduce the risk of cyanide poisoning. Processing operations such as fermentation, boiling/ cooking, and drying, applied to process food-containing cyanogenic glycosides have been reported to reduce cyanide content to acceptably safe levels (Bolarinwa *et al.*, 2016).

5. Conclusion

In conclusion, the phytochemical analysis of aqueous seed extracts of *Zingiberaceae aframomum melengueta* confirms the presence of important bioactive components and thus possesses valuable pharmacological health benefits.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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