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REVIEW ARTICLE

Alpinia zerumbet: A Review of the Chemistry, Quantity, and Pharmacological Properties of Selected Kavalactones

Eric Wei Chiang Chan[1*], Mio Kezuka[2], Hung Tuck Chan[2] and Siu Kuin Wong[3]

[1]Faculty of Applied Sciences, UCSI University, Cheras - 56000, Kuala Lumpur, Malaysia; chanwc@ucsiuniversity.edu.my

[2]Secretariat of International Society for Mangrove Ecosystems (ISME), Faculty of Agriculture, University of the Ryukyus, Okinawa - 9030129, Japan

[3]School of Foundation Studies, Xiamen University Malaysia, Sepang - 43900, Selangor, Malaysia

Abstract

Alpinia zerumbet or shell ginger is a ginger plant with diverse chemical constituents and medicinal and non-medicinal uses. Dihydro-5,6-dehydrokawain (DDK) and Dehydrokawain (DK) are two kavalactones (also known as kava pyrones or styrylpyrones) from *A. zerumbet*. Both DDK and DK have a carbonyl group at C2, a methoxy group at C4, and a double bond at C5 and C6. DK has a double bond at C7 and C8 that is absent in DDK. Quantity of DDK in *A. zerumbet* can be ranked as rhizome > leaf > flower > stem > seed. The pericarp and seed placenta of the fruit has higher quantity of DDK than the leaf. In most plant parts, the contents of DDK are higher than those of DK. Hispidin (HP) is synthesized from DK by hydrolysis. These three kavalactones from *A. zerumbet* have the most promising pharmacological properties that include insecticidal, fungicidal, antioxidant, inhibition of enzymes, inhibition of Advanced Glycation End-products (AGEs), inhibition of p21-activated kinase 1 (PAK1), inhibition of LIM domain kinase 1 (LIMK1), promotion of hair growth, anti-cancer, inhibition of melanogenesis, anti-inflammatory, anti-obesity, HIV-1 integrase inhibition, neuraminidase inhibition, osteogenic, anti-platelet aggregation, cytoprotective, anti-ulcerative, and singlet oxygen quenching activities. Some fields for further research are suggested. Sources of information in this review were from Google, Google Scholar, Science Direct, PubMed, J-Stage, China National Knowledge Infrastructure (CNKI), and PubChem.

Keywords: Dihydro-5,6-dehydrokawain, 5,6-Dehydrokawain, Hispidin

1. Introduction

Ginger plants (Zingiberaceae) of the genus *Alpinia* consist of over 250 species, occurring in tropical and sub-tropical countries of Asia and the Pacific with 51 species (35 endemic) in China[1,2]. Remarkable features of *Alpinia* species are the beauty of their inflorescences, and their wide use as ornament, medicine, and spice[3]. Major compounds reported in *Alpinia* species are diarylheptanoids, terpenoids, flavonoids, and phenylpropanoids. Pharmacological properties of *Alpinia* species include antioxidant, antibacterial, anti-fungal, antiviral, antiulcer, antiemetic, anti-anxiety, anti-cancer, anti-obesity, anti-inflammatory, hypoglycemic, gastroprotective, cardioprotective, and analgesic activities[2,4].

Alpinia zerumbet (Pers.) B.L. Burtt & R.M. Sm. or shell ginger, can grow up to 2–3 m tall[1,5]. *Alpinia speciosa*, *A. speciosum*, and *A. nutans* are synonyms of *A. zerumbet*. Plants have long, dark green, leathery, and aromatic leaves with velvety margins and clear midribs. Inflorescences bear shell-like flower buds in drooping clusters. Flower buds are attractive, milky white, and fragrant, with a pink apex. Open flowers have a conspicuous yellow labellum with red striations. Fruits are grooved capsules, bearing three compartments with more than 10 seeds

*Author for correspondence

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each[6]. Seeds are polyhedral, aromatic, and covered with a white membranous aril called a placenta. When rhizomes of *A. zerumbet* are cut, the flesh is cream-colored and emits a weak ginger aroma. A cultivar called *A. zerumbet* 'Variegata' has attractive variegated green leaves with yellow striations[5]. Photographs of the plants, inflorescences, fruits, seeds, and rhizome of *A. zerumbet* were taken from the grounds of the University of the Ryukyus in Senbaru, Okinawa, Japan (Figure 1).

The shell ginger grows naturally in East Asia. In China, *A. zerumbet* (*Yang San Jiang*) occurs in the southern provinces of Yunnan, Guangdong, Guangxi, and Hainan[1]. The species is common in Taiwan and on the Ryukyu islands of Japan. In Brazil, *A. zerumbet* (*Colonia* or *Pacová*) has been introduced, naturalized and has become an exotic plant. In Guizhou province, southwest China, the fruit of *A. zerumbet* is used by the Miao tribe to treat cardiovascular and gastrointestinal diseases[7,8]. In Okinawa, Japan, *A. zerumbet* (*Getto*) is an important commercial plant. Leaves of *Getto* are used to flavor noodles, to wrap rice cakes (*Mochi*) and the infusion is drunk as herbal tea[9]. Rhizomes are consumed as spices, and stem fibers are used to make paper, kariyushi wear, and textiles[10]. The essential oil distilled from *Getto* leaves has many uses such as cosmetics, soap, deodorant, perfume, skincare, and insect repellent[11]. In Taiwan, aboriginal tribes use the leaves of *A. zerumbet* for wrapping rice dumplings (*Zongzi*) and stem fibers for weaving into handicrafts[12]. In Brazil, the tea from *A. zerumbet* leaves is consumed as herbal tea with diuretic, anti-ulcerogenic, and hypotensive properties[13].

Medicinal properties of *A. zerumbet* are diverse and they include analgesic, anthelmintic, anti-aging, anti-atherogenic, anti-cancer, anti-depressant,

Figure 1. **(a).** A clump of *Alpinia zerumbet* plants, **(b).** inflorescences with open flowers, **(c).** young fruits, **(d).** mature fruits with seeds and placenta as inset, and **(e).** rhizome.

anti-glycation, anti-inflammatory, antimicrobial, anti-obesity, antioxidant, anti-platelet, anti-ulcerogenic, anxiolytic, cardioprotective, hair growth promotion, hypolipidemic, insecticidal, integrase inhibitory, lifespan prolongation, melanogenesis inhibitory, neuraminidase inhibitory, osteoblastic, osteogenic, thrombolytic, and tyrosinase inhibitory properties[5,8].

In this article, the chemistry, quantity, and pharmacological properties of selected kavalactones in *A. zerumbet* are reviewed. They include Dihydro-5,6-dehydrokawain (DDK), 5,6-Dehydrokawain (DK), and Hispidin (HP). Wherever relevant, terminologies used in pharmacology and their practical implications are explained for greater clarity.

2. Chemistry

Among the metabolites isolated from *A. zerumbet* are kavalactones (also known as kava pyrones or styrylpyrones). Of these, Dihydro-5,6-dehydrokawain (DDK) and Dehydrokawain (DK) have promising bioactive and pharmacological activities[14]. DDK and DK were first isolated from rhizomes[15], and subsequently from leaves and stems of *A. zerumbet*[13,16]. Based on their chemical structures, kavalactones can be classified into four types (A–D), depending on the presence or absence of a double-bond at C5 and C6, and/or at C7 and C8[14]. DDK, with a double bond at positions C5 and C6, belongs to type D, whereas DK, with two double bonds at both positions, belongs to type C (Figure 2).

Both DDK and DK have a carbonyl (C=O) group at C2 and a methoxy ($-OCH_3$) group at C4 of ring A. The C=O group at C2 and the oxygen atom of ring A constitute the α-pyrone ring. Hispidin (HP), not a natural kavalactone of *A. zerumbet*, is synthesized from DK by hydrolysis using stomach acid followed by metabolism with cytochrome P450 2C9 (CYP2C9) enzyme in microsomes of the rabbit liver[17,18]. HP has a chemical structure that is similar to that of DK except for three –OH groups at C4, C12, and C13. The molecular formula, molecular weight (g/mol), and IUPAC name of DDK, DK, and HP are as follows:

DDK	$C_{14}H_{14}O_3$	230	4-Methoxy-6 (2-phenylethyl)pyran-2-one
DK	$C_{14}H_{12}O_3$	228	4-Methoxy-6-[(*E*)-2 phenylethenyl]pyran-2-one
HP	$C_{13}H_{10}O_5$	246	6-[(*E*)-2-(3,4-Dihydroxyphenyl)ethenyl] -4-hydroxypyran-2-one

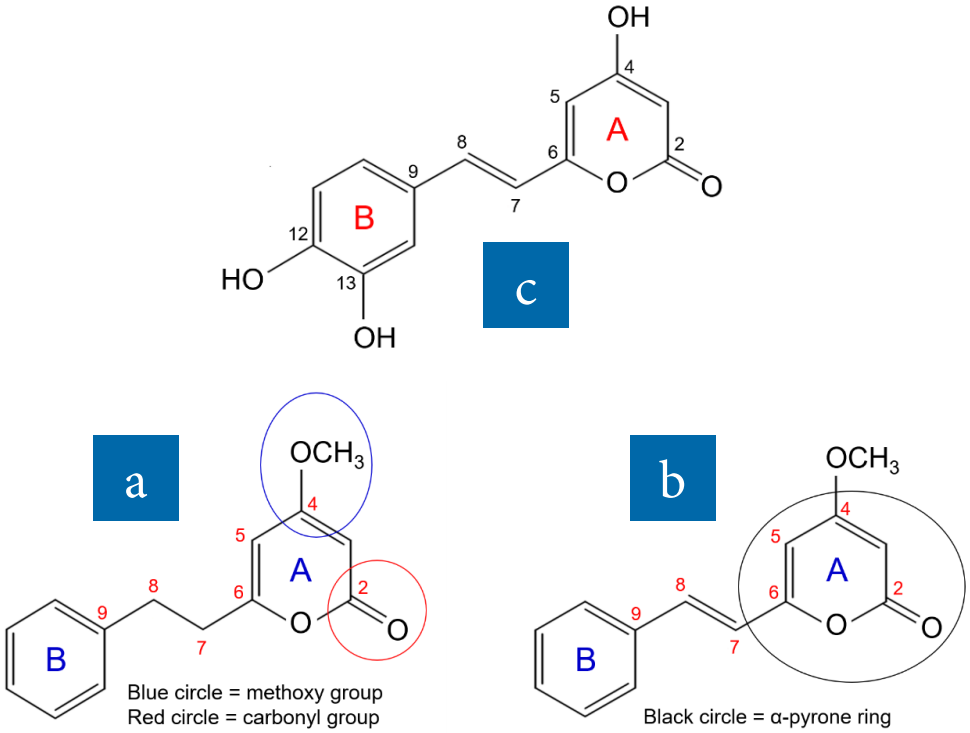

Figure 2. Molecular structures of **(a).** Dihydro-5,6-dehydrokawain, **(b).** 5,6-Dehydrokawain, and **(c).** Hispidin.

3. Quantity

DDK has been reported in the leaf, stem, rhizome, flower, seed, and placenta of *A. zerumbet*. DK has been reported in the leaf, stem, rhizome, and placenta. In the leaf, stem, and rhizome of *A. zerumbet* sampled from the grounds of the University of the Ryukyus, contents of DDK were 410, 80, and 350 mg/g, while contents of DK were 10, 20, and 100 mg/g, respectively[19]. Sampled from the same location, the leaf, rhizome, flower, and seed of *A. zerumbet* contain 149, 424, 340, and 3 mg/g of DDK, respectively[20,21]. Therefore, the ranking of DDK was: rhizome > flower > leaf > seed.

In hexane extracts, contents of DDK were highest in the flower (6.08 mg/g) > rhizome (5.41 mg/g) > stem (3.70 mg/g) > leaf (3.38 mg/g) > pericarp (0.13 mg/g) > seed (0.11 mg/g)[22]. Contents of DDK and DK in the rhizome, stem, leaf, flower, pericarp, and seed of *A. zerumbet* were compared. The quantity of DDK was highest in the aqueous pericarp extract (0.85 mg/g) followed by the aqueous rhizome extract (0.62 mg/g)[23]. The quantity of DK of the aqueous rhizome extract (1.23 mg/g) was the highest followed by the aqueous pericarp extract (1.15 mg/g) and the ethanol rhizome extract (1.14 mg/g).

Contents of DK were highest in the rhizome (3.13 mg/g) > flower (2.22 mg/g) > stem (2.08 mg/g) > leaf (1.67 mg/g) > pericarp (1.58 mg/g) > seed (0.22 mg/g). In the leaf, stem, and rhizome of *A. zerumbet*, contents of DDK were 410, 80, and 350 mg/g, while the quantity of DK was lower at 10, 20, and 100 mg/g, respectively[14]. Sampled from the Chosei Yakusou Headquarters in Okinawa, the ranking of DDK contents was pericarp (5.52 mg/g) > placenta (4.87 mg/g) > leaf (2.15 mg/g) while the ranking of DK contents was leaf (2.04 mg/g) > pericarp (1.56 mg/g) > placenta (1.32 mg/g)[24]. These studies showed that the contents of DDK in *A. zerumbet* can be ranked as: rhizome > leaf > flower > stem > seed. The pericarp and seed placenta of the fruit has higher contents of DDK than the leaf. In most plant parts, the contents of DDK are higher than those of DK.

Experiments with treatments on *A. zerumbet* plants yielded some interesting results. In the University of the Ryukyus, plants of two-month-old *A. zerumbet* were sprayed with 500 ml copper sulphate solution each, 24 h beforehand[25]. Treated plants extracted with chloroform yielded significantly higher contents of DDK (1104 µg/g) than non-treated plants (706 µg/g). In ethyl acetate extracts, there was no significant difference in the quantity of DDK between treated and non-treated plants. Recently, a study undertaken in Brazil showed that leaves of *A. zerumbet* sampled from Rio de Janeiro (6.63 mg/g) had higher content of DDK than leaves from Brasilia (1.84 mg/g)[26]. When leaves were dried for 17 h in the greenhouse at 40°C or for 7 days at room temperature, the content of DDK was lower at 1.40 and 1.25 mg/g, respectively.

4. Other Sources

DDK and DK have been isolated from other *Alpinia* species such as the rhizome of *A. formosa* (synonym *A. kumatake*)[27] and the seed of *A. blepharocalyx*.[28] DK has been identified in the fruit of *A. rafflesiana*[29], the rhizome of *A. malaccensis*[30], and the rhizome and seed of *A. mutica*[31,32]. Apart from *Alpinia* species, DDK and DK have been reported in other ginger species, e.g., the rhizome of *Boesenbergia rotunda*[33,34] and the rhizome of *Amomum uliginosum*[35].

Besides Zingiberaceae, DDK and DK are kavalactones found in the root of *Piper methysticum* (kava) of the family Piperaceae[14,36]. In the Pacific Islands, an aqueous infusion of kava roots is a popular beverage consumed by the local people for its sleep-inducing and narcotic effects.

HP has been reported in medicinal mushrooms of the genera *Phellinus* and *Inonotus*[37,38]. In *Phellinus linteus*, HP protected against peroxynitrite-mediated DNA damage and hydroxyl radical generation[39], protected against hydrogen peroxide (H_2O_2)-induced damage of pancreatic β-cells[40], displayed anti-inflammatory activity in lipopolysaccharide (LPS)-activated RAW264.7 cells[41], protected against acrylamide (AA)-induced oxidative stress in Caco-2 cells[42], inhibited β-secretase enzyme[43], and inhibited neuraminidase enzyme[44].

5. Pharmacological Properties

The pharmacological properties of DDK, DK, and HP from *A. zerumbet* are tabulated (Table 1) and described below:

Table 1. Pharmacological properties of DDK, DK, and HP from *Alpinia zerumbet*

No.	Bioactivity	Effect and Mechanism	Reference
1	Fungicidal	DDK displayed stronger antifungal activity than DK.	19
2	Antioxidant	DK exhibited stronger antioxidant activity than DDK.	23
3	Inhibition of enzymes	DK displayed stronger enzyme inhibitory activity than DDK.	23
4	Inhibition of AGEs	DK inhibited AGEs more strongly than DDK.	22
5	Inhibition of PAK1	The ranking of inhibition of oncogenic and aging-related PAK1 was HP > DK > DDK.	17
6	Inhibition of LIMK1	The ranking of inhibition of LIMK1) was HP > DDK > DK.	51
7	Promotion of hair growth	The ranking of hair cell growth promotion was HP > DK > DDK.	51
8	Anti-cancer	DK and HP were cytotoxic to certain cancer cells.	55, 56
9	Inhibition of melanogenesis	DDK, DK, and HP inhibited melanogenesis in melanoma cells, while DK inhibited mushroom tyrosinase activity.	57, 58
10	Anti-inflammatory	DDK and DK displayed comparable anti-inflammatory activity.	58
11	Anti-obesity	DDK, DK, and HP exhibited anti-obesity activity by inhibiting TG, ROS, and NO.	57
12	HIV-1 integrase inhibition	DDK and DK strongly inhibited the HIV-1 integrase enzyme.	59
13	Neuraminidase inhibition	DDK and DK displayed comparable inhibition of neuraminidase.	59
14	Osteogenic	DK promoted stronger osteogenic activity and osteoblastic differentiation in murine cells than DDK.	64-66
15	Anti-platelet aggregation	DK exhibited stronger anti-platelet aggregation and ATP release of rabbit platelets than DDK.	67
16	Cytoprotective	DDK and DK protected against H_2O_2-induced cytotoxicity in PC12 cells.	68, 69
17	Anti-ulcerative	DDK protected against gastric ulcers and inhibited gastric secretion.	70, 71
18	Singlet oxygen quenching	DDK exhibited singlet oxygen quenching activity.	72

Abbreviations: AGEs = advanced glycation end-products, ATP = adenosine triphosphate, DDK = dihydro-5,6-dehydrokawain, DK = dehydrokawain, HIV = human immunodeficiency virus, H_2O_2 = hydrogen peroxide, HP = hispidin, LIMK1 = LIM domain kinase 1, NO = nitric oxide, PAK1 = p21-activated kinase 1, ROS = reactive oxygen species, and TG = triglyceride.

5.1 Fungicidal

Studies on fungicidal effects of DDK and DK from *A. zerumbet* represented one of the earliest. Using the potato dextrose agar test assay, results showed that DDK and DK from *A. zerumbet* displayed antifungal effects towards pathogenic fungi *Pythium* sp. and *Corticium rolfsii*[19]. Growth inhibition of DDK was 72% and 64% at 100 ppm, while that of DK was 86% and 54% at 1000 ppm. This indicates that DDK has stronger antifungal activity than DK.

5.2 Antioxidant

DK from rhizomes of *A. zerumbet* showed stronger antioxidant activities than DDK based on 1,1-diphenyl-2-picrylhydrazyl (DPPH), 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) and phenazine methosulfate (PMS)-nicotinamide adenine dinucleotide (NADH) radical scavenging. IC_{50} values of DK were 122, 110, and 128 µg/ml, respectively[23].

5.3 Inhibition of enzymes

DK from rhizomes of *A. zerumbet* displayed stronger inhibitory activities against collagenase, elastase, hyaluronidase, and tyrosinase enzymes than DDK. IC_{50} values of DK were 24.9, 19.4, 19.5, and 76.7 µg/ml, respectively[23].

5.4 Inhibition of AGEs

Kavalactones from rhizomes of *A. zerumbet* inhibited Advanced Glycation End-products (AGEs) formation. DK exhibited stronger inhibition of Fructosamine Adduct (FA) than DDK with IC_{50} values of 360 and 673 µg/ml, respectively[22]. Inhibition of DK was also stronger than

DDK, based on glycation of Bovine Serum Albumin (BSA) and on glycation-induced protein oxidation. AGEs are compounds formed by reducing sugars such as glucose and have been implicated in diabetes and in age-related diseases such as eye, renal, atherosclerosis, and neurological disorders[45,46].

5.5 Inhibition of PAK1

The inhibition of p21-activated kinase 1 (PAK1) by kavalactones was measured using the adenosine diphosphate kinase assay. DDK and DK from rhizomes of A. zerumbet inhibited the oncogenic and aging-related PAK1 with IC_{50} values of 10 and 17 μM, respectively[17]. HP, a metabolite of DK, displayed stronger inhibition of PAK1 than DDK and DK with an IC_{50} value of 5.7 μM. PAK1 inhibition of HP was stronger than that of resveratrol (15 μM), used as the positive control. The ability of kavalactones to block the activities of PAK1 was attributed to their α-pyrone ring and methoxy group[17].

PAK1 is a protein kinase that is involved in multiple-signal pathways in mammalian cells[47,48]. This enzyme is responsible for diseases such as cancer, Acquired Immune Deficiency Syndrome (AIDS), Alzheimer's disease, inflammatory diseases, allergy, and diabetes. As an oncogenic kinase, PAK1 is involved in oncogenesis, tumor progression, and metastasis[49]. As an aging kinase, PAK1 promotes aging and shortens the organismal lifespan. PAK1 extended the lifespan of *Caenorhabditis elegans* by 60%[50], suggesting that PAK1 serves to regulate aging and longevity.

5.6 Inhibition of LIMK1

Inhibition of LIM domain kinase 1 (LIMK1) by DDK and DK from rhizomes of *A. zerumbet* based on IC_{50} values was 22 and 25 μM. Inhibition was better than resveratrol (37 μM), used as the positive control. HP displayed stronger inhibition against LIMK1 with an IC_{50} value of 14 μM[51]. LIMK1 is an oncogenic protein kinase responsible for normal development of the Central Nervous System (CNS)[52]. Removal of LIMK1 has been attributed to the development of human genetic disorders, including mental and neurodegenerative disorders, e.g., schizophrenia, autism, Alzheimer's disease, and Parkinson's disease[52,53].

5.7 Promotion of Hair Growth

DDK and DK from *A. zerumbet* promoted hair cell growth by 2.3-fold and by 2.6-fold at 100 μM, respectively[51]. HP stimulated hair cell growth by 2.1-fold at 10 μM. These results suggest that HP is the most potent and that PAK1 inhibitors could enhance the growth of hair cells. In a related study on hair growth, two non-kavalactones from *A. zerumbet*, namely, kaempferol-3-*O*-β-D-glucuronide and labdadiene, strongly increased the proliferation of Human Follicle Dermal Papilla Cells (HFDPC) by 117–180% and 132–226% at 10–100 μM, respectively[54].

5.8 Anti-cancer

DK from *A. zerumbet* leaves showed potent cytostatic activity to U-251 glioblastoma cells with an IC_{50} value of 0.25 μg/ml and total growth inhibition value of 4.43 μg/ml[55]. The weak anti-cancer activity was observed towards MCF-7 breast, K-562 leukemia, and NCI-H460 lung cancer cells with IC_{50} values of 2.85, 2.81, and 2.04 μg/ml. DK from flowers of *A. zerumbet* was cytotoxic to MCF-7 breast and HepG2 liver cancer cells with IC_{50} values of 3.1 and 6.8 μg/ml, respectively, but not to normal fibroblast cells[56]. HP, a metabolite of DK, inhibited the growth of A549 lung cancer cells, with an IC_{50} value of 25 μM[51].

5.9 Inhibition of Melanogenesis

DDK, DK, and HP from rhizomes of *A. zerumbet* inhibited melanogenesis in murine B16F10 melanoma cells[57]. At 50 μg/ml, DDK, DK, and HP inhibited melanin synthesis by 68%, 72%, and 63%, respectively. These values were stronger than kojic acid (positive control) which inhibited melanin synthesis by 51%. At 50 μg/ml, tyrosinase inhibition by DDK (55%), DK (74%), and HP (70%) is more potent than kojic acid (53%). It can be seen that these kavalactones are stronger melanin and tyrosinase inhibitors than kojic acid, a standard skin-lightening agent. From leaves of *A. zerumbet*, DK (but not DDK) inhibited the activity of mushroom tyrosinase with an IC_{50} value of 62 μg/ml[58].

5.10 Anti-inflammatory

From leaves of *A. zerumbet*, DDK and DK displayed anti-inflammatory activity by significantly inhibiting egg albumin denaturation, with comparable IC_{50} values of 14.5 μM and 14.9 μM, respectively. In addition, DK had stronger proteinase inhibitory activity (IC_{50} value of 39.9 μM) than DDK (IC_{50} value of 43.8 μM)[58]. From pericarps of *A. zerumbet*, DDK and DK inhibited Nitric Oxide (NO) in cytokinin interleukin-1β (IL-1β)-treated hepatocytes with IC_{50} values of 27.5 and 27.0 μM, respectively[24].

5.11 Anti-obesity

At 250 µg/ml, DDK and HP from rhizomes of *A. zerumbet* reduced the amount of intracellular triglyceride by 70% and 80%, respectively[18]. DDK, DK, and HP inhibited the production of Reactive Oxygen Species (ROS) and Nitric Oxide (NO) in 3T3-L1 adipocytes. At 20 µg/ml, DDK, DK, and HP inhibited ROS production by 42%, 44%, and 46%, respectively[57]. At the same concentration, NO production was strongly reduced by HP (72%) followed by DDK (57%) and DK (52%). These compounds are therefore potent antioxidants that inhibit both ROS and NO production.

5.12 HIV-1 Integrase Inhibition

DDK and DK from rhizomes of *A. zerumbet* strongly inhibited HIV-1 integrase (IN) enzyme with IC_{50} values of 4.4 and 3.6 mg/ml, respectively[59]. IN inhibition may be attributed to the α-pyrone group at ring A (Figure 2). IN, a 32-kDa protein with three structural domains, is indispensable for HIV-1 replication and has become a validated target for developing anti-AIDS agents[60]. Recently, IN inhibitors are a class of drugs approved for the treatment of HIV infection[61].

5.13 Neuraminidase Inhibition

DDK and DK from rhizomes of *A. zerumbet* inhibited neuraminidase with IC_{50} values of 24.6 and 25.5 µM[59]. It was reported that DDK is a reversible inhibitor of neuraminidase, with the methoxy group as its functionally active site. Neuraminidase is an enzyme that plays an essential role in influenza virus replication by promoting virus release from infected cells and subsequently facilitating virus spread within the respiratory tract[62]. Presently, neuraminidase inhibitors are a class of antiviral drugs for the treatment of influenza by inhibiting the enzyme[63].

5.14 Osteogenic

DDK and DK from rhizomes of *A. zerumbet* promoted osteoblastic differentiation of MC3T3-E1 murine cells, with DK having stronger activity based on alkaline phosphatase (ALP) activity and matrix mineralization[64]. At 80 µM, enhancement of ALP activity (25%) and matrix mineralization (71%) by DK was stronger than DDK (8% and 31%, respectively). Mechanisms involved increasing ALP activity and matrix mineralization. DK and its analogs exhibited osteogenic activity and inhibited osteoclastic differentiation of MC3T3-E1 cells[65]. Alkylation of ring A in DK is associated with stronger osteogenic activity. Fluorinated kavalactones inhibited osteoclastic differentiation of RAW264 cells by preventing osteoclastic bone resorption and inhibiting osteoclastogenesis[66].

5.15 Anti-platelet Aggregation

DK exhibited stronger anti-platelet aggregation and Adenosine Triphosphate (ATP) release of rabbit platelets than DDK with IC_{50} values of 60 and 10 µg/ml, respectively[67]. Aggregation of rabbit platelets was induced by arachidonic acid and collagen. The anti-platelet aggregation mechanism by DK and DDK may involve the inhibition of thromboxane A2, an inducer of platelet aggregation.

5.16 Cytoprotective

DDK and DK from pericarps of *A. zerumbet* reduced H_2O_2-induced cytotoxicity in PC12 rat adrenal medulla cells[68]. Protection of these neuronal cells may involve mechanisms such as activation of phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt), and inhibition of p38 Mitogen-Activated Protein Kinase (MAPK), oxidative stress, and caspase-3 activity. Among five kavalactones isolated from the leaves of *A. zerumbet*, aniba dimer A 3, aniba dimer C 4, and 6,6'-(3,4-diphenylcyclobutane-1,2-diyl)*bis*(4-methoxy-2*H*-pyran-2-one 5 protected human umbilical vein endothelial cells damaged by high glucose[69]. Protection by 3 and 4 was 83.1% and 58.2% at 12.5 µM, while that of 5 was 75.0% at 25 µM.

5.17 Anti-ulcerative

DDK isolated from the rhizome of *A. zerumbet* has been demonstrated to have a protective effect on experimental gastric ulcers (30–250 mg/kg) and can markedly inhibit gastric secretion (30–200 mg/kg)[70,71].

5.18 Singlet Oxygen Quenching

The singlet oxygen quenching activity of DDK from the leaf of *A. zerumbet* was found to be 57%, suggesting its ability to inhibit phototoxicity due to singlet oxygen formation[72].

6. Conclusion

It can be concluded that *A. zerumbet* is a multi-purpose ginger plant with promising medicinal and non-medicinal properties. Kavapyrones such as DDK, DK, and HP from this plant possess unique pharmacological properties such

as inhibition of AGEs, PAK1, LIMK1, HIV-1 integrase, and neuraminidase. Their practical implications in treating diseases such as diabetes, cancer, neurodegeneration, and HIV, and in promoting useful traits such as hair growth promotion, anti-aging, lifespan prolongation, and bone loss inhibition, present exciting fields for further research and will yield useful findings in the foreseeable future. At the same time, the commercial production of DDK, DK, and HP from *A. zerumbet* opens up industrial opportunities for these kavapyrones.

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