Alpinia zerumbet and Its Potential Use as an Herbal Medication for Atherosclerosis: Mechanistic Insights from Cell and Rodent Studies

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Keywords

Alpinia zerumbet · Atherosclerosis · Phytochemicals · Preventive effects

Abstract

Background/Aims: *Alpinia zerumbet* (Pers.) Burt. et Smith has been used as a flavor additive in food and a traditional medicine for centuries, especially in Guizhou Province, China, and it prolongs people's lives with multiple beneficial effects. Thus, one of the aims of this review was to expound the chemical constituents of this plant, especially its fruits. Since cardiovascular diseases, including atherosclerosis, pose a health threat to humans, another aim was to expound the possible mechanisms of its potential use as an herbal medication for atherosclerosis. **Methods:** In this study, 10 reports are cited to expound the potential bioactive compounds. Moreover, 33 reports explain the antihypertensive and anti-

atherosclerotic effects of the plant by ameliorating inflammation and endothelial dysfunction, increasing vasodilation, improving hyperlipidemia, downgrading the glucose status, and working as an antioxidant. **Results:** *A. zerumbet* is rich in terpenes, essential oils, flavonoids, polyphenolics, and sterols. Pharmacological experiments showed that *A. zerumbet* has antioxidative and anti-inflammatory effects on the NF- κ B signaling pathway and can ameliorate oxidative stress in the NOS-NO signaling pathway. Moreover, *A. zerumbet* demonstrates antihypertensive effects by accelerating vasorelaxant response and increasing 3T3-L1 intracellular cAMP, which has promising antiobesity properties, as well as hypolipidemic and anti-diabetic complication effects. **Conclusions:** *A. zerumbet* has potential functions and applications in the prevention of atherosclerosis, but further studies are required before clinical trials.

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Introduction

Alpinia zerumbet (Pers.) Burt. et Smith, which is also known as shell ginger or *yan-shan-jiang* in China, is native to East Asia and widely cultivated in tropical and subtropical zones of the world [1–3]. It has been used as a flavor additive in food and a traditional medicine for centuries. *A. zerumbet* seeds are used as folk medicine by the Miao ethnic group in Guizhou Province, China. *A. zerumbet* is also used as a dietary supplement in Japan, and it contributes significantly to prolonging human lives in the population of Okinawa [4]. Modern pharmacological research shows that *A. zerumbet* has important physiological and pharmacological functions, such as antioxidative [5, 6], antimicrobial [7], anticancer [8, 9], anti-inflammatory [10], antianxiety [11], and anti-cardiovascular disease [12] effects, and that it promotes osteoblastic cell differentiation activities [13].

Cardiovascular diseases can cause severe disability and premature death. About 17.3 million people die of cardiovascular diseases every year, accounting for 30% of global deaths [14]. Atherosclerosis is a common pathological abnormality and an exacerbated condition among a diverse group of cardiovascular diseases. The complex atherosclerotic process is generalized independently of age [15], and lasting microinflammation plays a crucial role in the pathogenesis of atherosclerosis and subsequent vascular damage [16]. Atherosclerosis is characterized by chronic systemic inflammation, lipoprotein retention, large atherosclerotic plaque formation, medium-sized arteries, and arterial wall remodeling [17, 18].

Atherosclerosis has been a threat to people's health, and the use of Chinese folk herbs for the prevention and treatment of atherosclerosis and other cardiovascular diseases has been emphasized. *A. zerumbet* (Pers.) Burt. et Smith belongs to the Zingiberaceae family, is a promising herb with active ingredients, and can be used for the prevention and treatment of cardiovascular disorders [19, 20]. In this review, reports on the potential bioactive compounds of *A. zerumbet* are collected from published scientific research, and the anti-inflammatory, antioxidative, antihypertensive, antiobesity, hypolipidemic, and anti-diabetic complication mechanisms of these potential bioactive compounds are investigated and surveyed. This review supports the role of *A. zerumbet* in the atherosclerotic process and increases the knowledge about the effects of this plant.

Potential Antiatherosclerotic Bioactive Compounds of *A. zerumbet*

A wide range of phytochemicals with biological effects were isolated from *A. zerumbet*. Essential oils are the most abundant components in *A. zerumbet*, and 17 common peaks were identified by Xiao et al. [21]. In essential oils from the fruits of nine batches of *A. zerumbet*, α -pinene (24.31%), β -pinene (21.31%), camphor (42.08%), and α -cadinol (27.16%) were the main bioactive ingredients. A total of 71 components were identified from essential oils extracted from flowers, accounting for 97.8–99.3%, the most abundant of which were eucalyptol (17.4–25.2%), terpinen-4-ol (Trp-4-ol; 14.7–22.6%), sabinene (7.0–16.5%), γ -terpinene (6.9–14.7%), *p*-cymene (2.1–8.8%), and α -terpinene (1.9–8.1%) [22].

Other active secondary metabolites of *A. zerumbet* include flavonoids and polyphenolics. Six polyphenolics – (1*E*,3*E*,5*E*)-6-methoxyhexa-1,3,5-trien-1-yl)-2,5-dihydrofuran (MTD), 5,6-dehydrokawain (DK), labdadiene, hispidin, dihydro-5,6-dehydrokawain (DDK), and (*E*)-2,2,3,3-tetramethyl-8-methylene-7-(oct-6-en-1-yl)octahydro-1*H*-quinolizine (TMOQ) – were isolated from *A. zerumbet* rhizomes or seeds, which could be potentially useful for the prevention or treatment of hyperpigmentation and obesity [23, 24]. A total of 10 compounds – dihydro-5,6-dehydrogenated capsaicin, astragalin, quercetin-3-*O*- β -D-glucoside, digalactosyldiacylglycerol, quercetin-3-*O*- β -D-glucuronide, 4',6'-dihydroxy-2'-methoxyl dihydrochalcone, cardamomin, anibadimer A, 1-*p*-menthene-3,6-diol, and β -sitosterol – were isolated from the leaves of *A. zerumbet* [25]. An agglutinin with a molecular mass of 130 kDa and zerumbone, which can inhibit platelet aggregation, were isolated from *A. zerumbet* seeds and rhizomes, respectively [26, 27]. Ghareeb et al. [20] identified 37 profiles of polyphenolics from the leaves of *A. zerumbet* using high-performance liquid chromatography-electrospray ionization mass spectrometry, including flavonoids (aglycones and glycosides) and benzoic and cinnamic acid derivatives, which demonstrate satisfactory anti-inflammatory, antinociceptive, and antipyretic effects in vivo. Epicatechin, kaempferol-3-*O*-glucuronide, rutin, and kaempferol-3-*O*-rutinoside were isolated from leaves, seeds, and rhizomes of *A. zerumbet*, which exhibit a broad spectrum of bioactivities, including antiemetic, antiulcerative, antibacterial, anti-inflammatory, antiemetic, anticancer, antioxidative, hepatoprotective, and antinociceptive processes [2, 28, 29].

Volatile compounds and other secondary metabolites play important roles as signaling compounds against ox-

Table 1. Dosages and model responses to pharmaceutical and biological activities of *Alpinia zerumbet*

Activity	Extracts and compounds	Dosage	Time	Models	Ref.
Anti-inflammatory	Essential oils (1,8-cineole) extracted from fructus <i>A. zerumbet</i>	300 mg/kg (orally administered)	7 days	LPS-induced male Kunming mice	[36]
	EOFAZ	0.25, 1.0, 4 µg/mL	1 h	HUVECs	[38]
	1,8-Cineole	0.14, 0.57, 2.27 µM	1.5 h	HUVECs	[39]
Antioxidant	EOFAZ	1, 2, or 4 µg/mL	2 h	HAECs	[43]
	EOFAZ	1, 2, or 4 µg/mL	2 h	HAECs	[44]
	EOFAZ	0.1 mg/L	0.5 h	HUVECs	[45]
	Steroidal compounds	IC ₅₀ = 2.30±0.02 µg/mL IC ₅₀ = 5.00±0.07 µg/mL IC ₅₀ = 1.29±0.07 µg/mL IC ₅₀ = 15.40±0.86 µg/mL	15 min 15 min 5 min 24 h	Anti-tyrosinase activity Pancreatic lipase inhibition Lipoxygenase inhibition LDL oxidation inhibition	[46]
Antihypertensive	MFEOAz	0.1–3,000 µg/mL	30 min	Rat thoracic aorta	[1]
	MFEOAz	100 and 300 µg/mL (intragastric administration)	30 days	Male Wistar rats	[1]
	EOFAZ	0.01–3,000 mg/mL	5 min	Rat aortic rings	[48]
	1,8-Cineole	0.0000647–19.5 mM	5 min	Rat aortic rings	[48]
	Hydroalcoholic extracts from the leaves of <i>A. zerumbet</i>	1–30 µg 50 mg/kg	3 min 28 days	Rat superior mesenteric vascular bed Male Wistar rats	[49]
Antiobesity	DDK, DK, hispidin	100 and 250 µg/mL	72 h	3T3-L1 adipocytes	[55]
Hypolipidemic	ASP, ASH, and ASO	ASP (1, 3, and 5%), ASH (1, 3, and 5%), and ASO (0.01, 0.05, and 0.10%)-fortified diets	8 weeks	Male Syrian hamsters	[3]
	Aqueous extract of <i>A. zerumbet</i> seed powder	0.5–20 mg/mL	36 h	Lipid micelles	[57]
	Ethanol extract of fresh <i>A. zerumbet</i> seed powder	0.5–20 mg/mL	36 h	Lipid micelle	[57]
	SP	High-fat with high-cholesterol diet plus SP (1, 3, and 5%)	8 weeks	Male Syrian hamsters	[57]
	SO	High-fat with high-cholesterol diet plus SO (0.01, 0.05, and 0.1%)	8 weeks	Male Syrian hamsters	[57]
Anti-diabetic complication	DK	IC ₅₀ = 360 µg/mL	30 min	Fructosamine adducts	[60]
	DDK	IC ₅₀ = 673 µg/mL	1 h	α-Dicarbonyl formations	
	Labdadiene	IC ₅₀ = 51.06 µg/mL			

LPS, lipopolysaccharide; EOFAZ, essential oils extracted from fructus *A. zerumbet*; HUVECs, human umbilical vein endothelial cells; HAECs, human aortic endothelial cells; LDL, low-density lipoprotein; MFEOAz, methanolic fraction of the essential oil of *A. zerumbet*; DDK, dihydro-5,6-dehydrokawain; DK, 5,6-dehydrokawain; ASP, *A. seed powder*; ASH, *A. seed powder/husk*; ASO, *A. seed essential oil*; SP, *A. zerumbet seed powder*; SO, *A. zerumbet seed essential oils*.

idative stress, which may reflect beneficial health effects [30, 31]. Thus, the active ingredients of *A. zerumbet*, with satisfactory antioxidative, anti-inflammatory, antihyperglycemic, hypotensive, and hypolipidemic properties, have antiatherosclerotic effects.

Effects of *A. zerumbet* on Atherosclerosis

Microinflammation plays a crucial role in the pathogenesis of atherosclerosis and subsequent vascular damage [32, 33]. The pathological process of atherosclerosis

is complex, and risk factors include dyslipidemia, hyperglycemia, and/or diabetes mellitus, obesity and/or unbalanced nutrition, hypertension, sedentariness, smoking, permanent stress, and environmental factors [16]. In Table 1, doses as well as model responses to pharmaceutical and biological activities of *A. zerumbet* are listed.

Anti-Inflammatory Effect of A. zerumbet

Inflammation plays a crucial role in endothelial dysfunction, as well as in the occurrence and development of cardiovascular diseases, specifically, in atherosclerosis [34]. Atherosclerosis is characterized by excessive fibrosis in the intima and fatty plaque formation caused by the accumulation of predominantly low-density lipoprotein (LDL) cholesterol; by the proliferation of smooth muscle cells caused by increased oxidative stress and/or cytokines; and by the infiltration and/or migration of a group of cells such as monocytes, T cells, and platelets, which are formed in response to progressing microinflammation [35]. Essential oils extracted from fructus *A. zerumbet* (EOFAZ) demonstrate strong anti-inflammatory effects in vivo and in vitro [36].

NF- κ B and TLR4-dependent NF- κ B signaling regulate inflammation and contribute to the development of lipopolysaccharide (LPS)-induced or high-glucose-induced inflammation [37]. EOFAZ show significant protective effects on LPS-induced human aortic endothelial cell (HAEC) activation and inhibitory effects against inflammation and injury by suppressing TLR4/NF- κ B signaling in vitro and in vivo. EOFAZ (50 and 100 ng/mL) can reverse the effect of LPS on the mRNA and protein levels of vascular cell adhesion molecule-1 (VCAM-1) in primary HAECs in vitro. In addition, it can prevent the effects of LPS on IKK α / β phosphorylation and I κ B α protein levels by abolishing the LPS-induced activation of NF- κ B signaling [20]. Furthermore, EOFAZ exhibit satisfactory protection against LPS-induced HAEC activation and inflammation by modulating TLR4 expression. The cell viability increases with EOFAZ, lactic acid dehydrogenase (LDH) release is abolished, and apoptosis inhibition through an increase in caspase-3 is prevented.

EOFAZ can reduce p65/DNA binding to inhibit NF- κ B activation induced by high glucose [38] when human umbilical vein endothelial cells (HUVECs) are pretreated with EOFAZ at 0.25, 1.0, or 4 μ g/mL for 1 h and exposed to indicated concentrations of glucose (35 mM) for 24 h. The findings of the study showed that LDH leakage levels decrease and the inflammatory cytokines TNF- α and IL-8 are reduced in a dose-dependent manner. The translocation of the p65 subunit of NF- κ B, as well as the expression

of ICAM-1 and VCAM-1, is also inhibited significantly by EOFAZ.

1,8-Cineole is the key active substance in EOFAZ, which can ameliorate HUVEC injury by suppressing NF- κ B signaling in vitro [39]. Results have revealed that when HUVECs are preincubated with 1,8-cineole (0.14, 0.57, or 2.27 μ M) for 1.5 h and then exposed to LPS (2.5 μ g/mL) for 12 h, the level of LDH leakage is reduced significantly, and cell morphology returns to nearly normal levels as assessed via hematoxylin and eosin staining. Moreover, the inflammatory cytokines IL-6 and IL-8 are downregulated in a dose-dependent manner through the NF- κ B signaling pathway, accompanied simultaneously by reduced phosphorylation of NF- κ B p65, reduced production of iNOS, and recovered eNOS expression.

Antioxidant Effect of A. zerumbet

Increasing evidence suggests that stress from the imbalanced production and elimination of reactive oxygen species (ROS) is involved in the pathophysiology of atherosclerosis [40]. The progression of atherosclerosis involves endothelial damage, LDL deposition and oxidation, and fibrous plaque formation [41]. In addition, apoptosis of intraplaque small vessels, including endothelial cells, has been implicated in the pathogenesis of atherosclerosis [42]. EOFAZ can significantly inhibit ox-LDL-induced endothelial dysfunction in HAECs via the Akt/NOS-NO signaling pathway, and the results indicate that unbalanced NOS-NO bioavailability is involved in oxidative stress to a certain degree [43]. HAECs are pretreated with EOFAZ (1, 2, or 4 μ g/mL) for 2 h and coincubated with ox-LDL (150 μ g/mL) for another 12 or 24 h. The results confirm that EOFAZ inhibit LDH release in a dose-dependent manner, especially in high-dosage groups. Mitochondrial membrane potential damage and ROS production are improved after cells are preincubated with EOFAZ in ox-LDL-induced cells. As a major causative factor in the development of atherosclerosis, NO is markedly increased by pretreatment with EOFAZ. The endothelial protection of EOFAZ suppresses mRNA and protein expression of Akt, eNOS, and soluble guanylate cyclase, with a positive dose-dependent relationship, and iNOS is decreased significantly, combined with an upregulation of p-Akt, eNOS, and soluble guanylate cyclase expression and a downregulation of iNOS expression, when pretreated with EOFAZ (2 μ g/mL).

EOFAZ can resist ox-LDL-induced oxidative stress and apoptosis [44]. HAEC viability is increased and cell morphological alterations are ameliorated by pretreat-

ment with EOFAZ (1, 2, or 4 $\mu\text{g/mL}$) for 2 h and exposure to 150 $\mu\text{g/mL}$ LDL for 24 h. In addition, TUNEL- or Hoechst 33258-staining-positive cells are abrogated by EOFAZ after ox-LDL stimulation. EOFAZ can also downregulate the mRNA and protein expression levels of Bax and caspase-3. Furthermore, upregulation of Bcl-2 protein and mRNA levels is observed in cells with EOFAZ, which can attenuate ox-LDL-induced HAEC apoptosis.

Shen et al. [45] demonstrated the prevention of ox-LDL-induced endothelial cell injury by EOFAZ-ameliorated cellular redox status. HUVECs were preincubated with 0.1 mg/L of EOFAZ for 0.5 h and then exposed to 100 mg/L of ox-LDL for 24 h. An MTT assay showed that EOFAZ can restore cell viability, trypan blue exclusion staining, and LDH release. Under oxidative stress, EOFAZ can increase the glutathione content, decrease the malondialdehyde content, and ameliorate antioxidant enzyme activities, such as superoxide dismutase, catalase, and glutathione peroxidase in cell lysates.

Steroidal compounds from the rhizomes, stems, leaves, flowers, pericarps, and seeds of *A. zerumbet* also exhibit strong inhibitory LDL oxidation in vitro. Seed extracts demonstrate the strongest effect against tyrosinase ($\text{IC}_{50} = 2.30 \pm 0.02 \mu\text{g/mL}$), pancreatic lipase ($\text{IC}_{50} = 5.00 \pm 0.07 \mu\text{g/mL}$), 15-lipoxygenase ($\text{IC}_{50} = 1.29 \pm 0.07 \mu\text{g/mL}$), and LDL oxidation activities ($\text{IC}_{50} = 15.40 \pm 0.86 \mu\text{g/mL}$), and most of the extracts, except those from the stem, show partial agonistic properties toward estrogenic activity at 500 $\mu\text{g/mL}$ [46]. The bioactivity of the extracts may be related to cholest-4-ene-3,6-dione, sitosterol, stigmasterol, and campesterol compounds, and cholest-4-ene-3,6-dione is the main substance present only in seed extracts.

Experimental Antihypertensive Effect of A. zerumbet

Hypertension is a major risk factor in atherosclerosis [16, 47]. However, favorable antihypertensive effects of *A. zerumbet* have been reported [1]. The methanolic fraction of the essential oil of *A. zerumbet* (MFEOAz) at 0.1–3,000 $\mu\text{g/mL}$ can induce vasorelaxant responses against phenylephrine and KCl-induced contraction in rat aortic rings in vitro in a concentration-dependent manner by inhibiting NO synthesis, which is an indirect measurement of blood pressure. With a Ca^{2+} -free Krebs solution or caffeine-induced contraction, preincubation with MFEOAz (100 and 300 $\mu\text{g/mL}$) can attenuate tension induced by phenylephrine. The in vitro vasorelaxation properties of MFEOAz are also confirmed in the intragastric administration of MFEOAz in vivo. The results suggest that MFEOAz can induce relaxation in rat aortic

rings by inhibiting calcium influx via voltage- and receptor-operated calcium channels and inhibit calcium mobilization from intracellular stores.

Pinto et al. [48] reported the endothelium-dependent vasorelaxant effects of EOFAZ and 1,8-cineole in rats. In phenylephrine-induced contraction, 0.01–3,000 mg/mL of EOFAZ can result in incomplete relaxation in isolated aorta preparations with an intact endothelium. Correspondingly, 1,8-cineole with a 0.0000647- to 19.5-mM concentration can induce complete vasorelaxant effects ($\text{IC}_{50} = 663.2 \pm 63.8 \text{ mg/mL}$) and significantly reduce endothelium-denuded rings without the effect of tetraethylammonium chloride or indomethacin in a bath. The popular and potential uses of *A. zerumbet* for the treatment of hypertension were corroborated.

Hydroalcoholic extracts obtained from the leaves of *A. zerumbet* (AZE) indicate antihypertensive and endothelium-dependent vasodilator effects in the mesenteric vascular bed and deoxycorticosterone acetate (DOCA)-salt hypertension in rats [49]. Norepinephrine- (6–30 mM) or phenylephrine-precontracted (10–30 mM) rats were injected with AZE (1–30 mg), and endothelium-dependent vasodilation in the mesenteric vascular bed was induced. Vasodilation was unchanged by 4-aminopyridine (inhibitor of voltage-dependent K^{+} channels), glibenclamide (inhibitor of the ATP-dependent K^{+} channel), or charybdotoxin plus apamin, which suggests that an independent activation of ATP-, voltage-, and calcium-dependent K^{+} channels and bradykinin receptors may not be involved in the antihypertensive mechanism of AZE. However, the effect can be reduced by L-NAME (inhibitor of NO synthase) or ODQ (inhibitor of guanylyl cyclase), which also suggests that AZE vasodilation is involved in the NO-cyclic guanosine monophosphate pathway. In rats with DOCA-salt hypertension, chronic oral administration of AZE can induce a significant reduction in systolic, mean, and diastolic arterial pressure.

EOFAZ and Trp-4-ol (a key bioactive ingredient) demonstrate antihypertensive effects in DOCA-salt-hypertensive rats [50, 51]. EOFaz (1–20 mg/kg) or Trp-4-ol (1–10 mg/kg) decreases mean aortic pressure dose-dependently in uninephrectomized and DOCA-salt-hypertensive rats. Hypotensive responses evoked by Trp-4-ol are significantly greater than those evoked by EOFaz, and the same effects also appear in conscious rats. However, under ganglionic blockade by hexamethonium, EOFaz can decrease mean aortic pressure in rats. The mechanism in this hypertensive model involves vascular smooth muscle relaxation rather than enhanced sympathetic nervous system activity.

Experimental Antiobesity Effect of A. zerumbet

Obesity is a leading metabolic disease and closely associated with coronary heart disease, hypertension, type 2 diabetes mellitus, cancer, respiratory complications, and osteoarthritis [52, 53]. A plethora of mechanisms underline the relationship between obesity and atherosclerosis. Obesity is an independent major risk factor for atherosclerotic vascular disease and cardiometabolic syndrome [54]. 3T3-L1 adipocytes are used to investigate the antiobesity activity of DDK, DK, and hispidin, which are metabolites of DK [55]. These compounds do not reduce 3T3-L1 adipocyte viability but rather significantly increase intracellular cAMP (cyclic adenosine monophosphate) concentrations by $81.2 \pm 0.06\%$, $67.0 \pm 1.62\%$, and $56.9 \pm 0.19\%$, respectively, and inhibit glycerol-3-phosphate dehydrogenase and pancreatic lipase, with hispidin and DDK as the most potent inhibitors. At $250 \mu\text{g/mL}$, hispidin also stimulates glycerol release by $276.4 \pm 0.8\%$ and inhibits lipid accumulation by $47.8 \pm 0.16\%$. At $250 \mu\text{g/mL}$, hispidin and DDK decrease the intracellular triglyceride content by $79.5 \pm 1.37\%$ and $70.2 \pm 1.4\%$, respectively. Thus, these compounds have promising antiobesity properties.

Experimental Hypolipidemic Effect of A. zerumbet

Circulating cholesterol irritates and weakens the endothelial lining, thereby eventually penetrating the arterial wall and accelerating the progression of atherosclerosis [56]. In an experiment, male Syrian hamsters with increased fecal neutral cholesterol were fed with *Alpinia* seed powder, *Alpinia* seed powder/husk, and *Alpinia* seed essential oil. The serum total triglyceride and LDL serum levels were significantly reduced, and the high-density lipoprotein (HDL) and arachidonic acid levels were increased, compared with a high-fat group [3]. At dosages of $0.5\text{--}20 \text{ mg/mL}$, an aqueous extract of *A. zerumbet* seed powder and an ethanolic extract of fresh *A. zerumbet* seed powder suppressed lipid peroxidation for 36 h, and Lin et al. [57] also found that powder and essential oils from *A. zerumbet* seed were effective hypolipidemics in male Syrian hamsters. Moreover, the seed demonstrated serum total triglyceride-decreasing, serum total cholesterol-increasing, and amazingly potent HDL cholesterol (C)-elevating capabilities by modifying ratios of LDL-C/HDL-C [57]. These results suggest that *A. zerumbet* has promising potent hypolipidemic bioactivity.

Experimental Anti-Diabetic Complication Effect of A. zerumbet

Ameliorating diabetes-induced atherosclerotic cardiovascular disease is a considerable challenge for clinicians.

The regulation of glucose metabolism and development of atherosclerosis through the modulation of peripheral vascular functions plays an important role in the treatment of atherosclerosis [58]. Advanced glycation end products (AGEs) are a complex and heterogeneous group of compounds that have been implicated in diabetes-related complications. AGEs are closely associated with hyperglycemia, and their pathobiochemistry can explain many of the changes in diabetes-related complications [59]. The inhibition of fructosamine adducts and α -dicarbonyl formations can reduce AGE formation and lessen the chance of diabetic complications. Chompoo et al. [60] investigated the inhibitory activities of DK, DDK, and 8(17),12-labdadiene-15,16-dial (labdadiene) compounds from the hexane extracts of various parts of *A. zerumbet* on fructosamine adducts and α -dicarbonyl formations using an NBT assay. The results showed threefold inhibitory properties of these compounds against AGE formation. Among these properties, labdadiene demonstrated a stronger inhibiting activity ($\text{IC}_{50} = 51.06 \mu\text{g/mL}$) on fructosamine adducts than DK ($\text{IC}_{50} = 360 \mu\text{g/mL}$) and DDK ($\text{IC}_{50} = 673 \mu\text{g/mL}$). The same was observed for the inhibitory effect on α -dicarbonyl formations, which suggests labdadiene has a stronger effect than DK and DDK. It is a potent antiglycation agent and can be used to inhibit glycation-associated complications in diabetes.

Conclusions

A. zerumbet, as a medicinal plant, has potential functions and applications in atherosclerosis. Essential oils and secondary metabolites from its flowers, leaves, rhizomes, and seeds demonstrate antioxidative and anti-inflammatory effects on the NF- κ B signaling pathway and can ameliorate oxidative stress in the NOS-NO signaling pathway. Moreover, *A. zerumbet* shows antihypertensive effects by accelerating the vasorelaxant response and increasing 3T3-L1 intracellular cAMP, which has promising antiobesity properties, as well as hypolipidemic and anti-diabetic complication effects. *A. zerumbet* interacts favorably with the risk factors for atherosclerosis and can contribute to the prevention of atherosclerosis. However, the main compounds responsible for atherosclerosis are not well understood. Data on the dosage, kinetic study and duration of use of *A. zerumbet* in therapy, as well as clinical experience in prospective research, are absent. Thus, investigating the antiatherosclerotic effects of *A. zerumbet* is a considerable but necessary challenge for future studies.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

The first author Ting Xiao designed and wrote the manuscript; Jiaoyan Huang, Xiaowei Wang, and Linjing Wu consulted the literature; Xue Zhou, Feng Jiang, Zhiyong He, and Qianqian Guo conducted data collection and analysis; Ling Tao and Xiangchun Shen provided essential materials and modified and validated the manuscript; and all authors read and approved the final manuscript.

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