Alpha glucosidase inhibitory activity of the *Zingiber zerumbet* Linn rhizomes

Le Thi Thuy Loan [1], Dang Thi Thuy My [2], Dang Dinh Thanh [3], Dam Thi Bich Hanh [4*]
[1-2, 4] Tay Nguyen University, Vietnam
[3] Buon Ma Thuot Medical University, Vietnam

* Corresponding Author: **Dam Thi Bich Hanh**

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Abstract
The total methanol residue, *n*-hexane and chloroform extracts from *Zingiber zerumbet* Linn rhizomes have been evaluated for *α*-glucosidase inhibitory activity in an attempt to identify potential active ingredients in natural products. The results showed that the chloroform extract inhibited *α*-glucosidase more effectively than the positive control acarbose, with an IC_{50} value of 126.9 *μ*g/mL. Chemical investigation of the chloroform extract led to the isolation of naringenin (1). The compound 1 expressed strong *α*-glucosidase inhibitory activity with respective IC_{50} values of 19.6 *μ*M, which are two-fold and eleven-fold lower than that of acarbose (IC_{50} 214.1 *μ*M). The research demonstrated the *α*-glucosidase inhibitory activity of the *Zingiber zerumbet* Linn rhizome as potential antidiabetic agents.

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1. Introduction

Zingiber zerumbet Linn Smith (*Z. zerumbet*), a member of the family Zingiberaceae, is widely cultivated throughout the tropical areas including Southeast Asia, Korea, India, Thailand, Bangladesh, etc., due to its potentially medicinal properties [1-3]. The plant is perennial, grows to about 1-1.3 meters tall with short stems which are usually be replaced by pseudostems formed by leaf sheaths. Its rhizomes have been regularly used as food flavouring and appetizer in various countries' cuisines while the rhizomes extracts have been used traditional medicine as a cure for swelling, loss of appetite, lumbago, diabetes, inflammation, chest pain, rheumatic pains, bronchitis, dyspepsia and sore throat [4-7].

In traditional Vietnamese medicine, Z. zerumbet is characterized by its bitter taste, neutral properties, and spicy flavor. It is valued for its ability to expel wind and cold, alleviate pain, and improve blood circulation, making it a common choice for remedies aimed at stimulating, toning, and detoxifying the body. *Z. zerumbet* is also used to treat ailments such as dizziness, nausea, fainting, and windstroke. It is particularly recognized for its detoxifying effects, postnatal recovery benefits, and its role in enhancing digestion [8].

From the pharmacological point of view, *Z. zerumbet* has been reported to inhibit colon and lung carcinogenesis in mice [9], CXCL12-induced invasion of breast and pancreatic tumor cells [10], apoptosis in liver cancer [11], suppress phorbol ester-induced expression of multiple scavenger receptor genes in THP-1 human monocytic cells and Epstein-Barr Virus activation [12-13]. Previous studies on the chemical composition of *Z. zerumbet* have identified various bioactive compounds such as: zerumbone, borneol, *α*-pinene, *β*-pinene, camphor, linalool, limonene, *α*-curcumene, *α*-humulene, humulene monoxide, humulene dioxide, *β*-caryophyllene, camphene, cineole [14] and new sesquiterpenoids such as humulene epoxide I, humulene epoxide II, humulene epoxide III, humulenol I, humulenol II, and caryophyllene oxide found in the essential oil of Indian *Z. zerumbet* rhizomes [14-16]. Additionally, some new compounds have been identified in the essential oil of *Z. zerumbet* including *cis*-nerolidol, *α*-phellandrene, terpinolene, *p*-cymene, caryophyllene oxide, *δ*-cardinene, fenchone, and bornyl acetate [17]. Phenolic compounds and glycosides have also been found, including zerumbone, 3-*O*-methyl kaempferol, kaempferol-3-*O*-(2,4-di-O-acetyl-α-L-rhamnopyranoside), and kaempferol-3-*O*-(3,4-di-*O*-acetyl-α-L-rhamnopyranoside) from ginger rhizomes [18].

Among the bioactive compound isolated from *Z. zerumbet*, zerumbone is the only compound that has been studied extensively. Zerumbone revealed *in vivo* antinociceptive [19] and anti-inflammatory [20-23] and antiplatelet aggregation [24] activities.

In our effort to find out plants with potential acitivity for treating diabetes, *Z. zerumbet* is a commonly known plant that contains many bioactive compounds capable of inhibiting α-glucosidase, making it a subject of growing research interest. Here in, we discribes the study on *Z. zerumbet* collected in a Giang province icluding collecting extracts from rhizomes of *Z. zerumbet*, isolating and identifying the chemical constituents of chloroform extract. The potential inhibitory against α-glucosidase of the obtained extracts and isolated compounds have also been assessed.

2. Materials and Methods

2.1. General

Column chromatography (CC) was conducted on silica gel 60 (Merck, 15–40 μm, 40–63 μm and 63–200 μm). Thin layer chromatography (TLC) was carried out on precoated plates of silica gel 60 F254 (Merck) and spots were visualised using UV light (254 and 365 nm) or staining with vanilin-H_2SO_4 10% solution and heating for 2–3 min. The UV spectra were recorded on a V-630 UV-VIS spectrophotometer (Jasco, Japan). NMR spectra were measured on a Bruker Avance 500 MHz NMR spectrometer, operating at 500 MHz (^{1}H) and 125 MHz (^{13}C) with TMS as an internal standard. Chemical shifts were recorded in parts per million δ (ppm).

2.2. Plant materials

The whole plant of *Z. zerumbet* was collected in a Giang Province, Vietnam, and identified by Quoc-Binh Nguyen, Ph.D., Vietnam National Museum of Nature, Vietnam Academy of Science and Technology (VAST). The voucher specimen (GG-AG-01) was carefully stored at the Faculty of Natural Science and Technology, Tay Nguyen University, Buon Ma Thuot City, Dak Lak Province, Vietnam

2.3. Extraction and isolation

The rhizomes were washed, cut into small pieces and dried in the oven at the temperature of 40 ºC in three days to obtain 5.9 kg dried sample. The dried sample was extracted with methanol (MeOH) (2.5 L × 3) at room temperature using conventional ultrasound-assisted technique. The extracting solution was then collected and evaporated under reduced pressure to yield 618.5 g methanol residue. The methanol residue was partitioned sequentially with solvents in the order of increasing polarity as following: *n*-hexane, chloroform, ethyl acetate (each solvent 3 L × 3). Concentration of the extracted solutions afforded *n*-hexane extract (140.0 g), chloroform (69.0 g), ethyl acetate extract (18.1 g), and methanol extract (370.0 g).

The chloroform extract was loaded onto silica gel chromatography column (CC) eluted with a gradient solvent system of chloroform-methanol (100:0 to 0:100, v/v) to afford 11 fractions A-K. Fraction E was fractionated by employing CC over silica gel, eluting with a gradient of *n*-hexane-acetone (70:1 to 0:100, v/v) to obtain thirteen subfractions, E1-E13.

Subfraction E9 was separated on silica gel CC using a gradient solvent system of chloroform-ethyl acetate (100:0 to 0:100, v/v) to yield eight subfractions: E9.1 (29.5 mg), E9.2 (48.6 mg), E9.3 (9.8 mg), E9.4 (71.3 mg), E9.5 (26.7 mg) and E9.6 (8.8 mg). Subfraction E9.1 was purified by using thin-layer chromatography eluted with chloroform-acetone (7.5:2.5, v/v) to obtain compound 1 (7.2 mg).

2.4. Inhibition of α-glucosidase assay

The α-glucosidase inhibitory protocol was carried out according to previously assay with slight modification [25]. Extracts and compounds were dissolved in DMSO and diluted with phosphate buffer (pH 6.8) to various concentrations of 250, 100, 50, 25 and 10 μg/ml. In a 96-well plate, a reaction mixture containing 100 μL of phosphate buffer (100 mM, pH 6.8), 40 μL of extracts or compounds, 20 μL α-glucosidase (0.4 U/mL, CAS No 9001-42-7, Sigma) were pre-incubated for 15 min at 37 °C. Then, 40 μL substrate *p*-nitrophenyl-α-D-glucopyranoside (pNPG, 2.5 mM, CAS No 3767-28-0, Sigma) were added to the mixture. The reaction was stopped by 100 μL of Na_2CO_3 (0.1 M) for each well after 20 min incubation. Without test compound was set up as a blank control and acarbose was used as a positive control. Experiments were done in triplicates. The absorbance of the released *p*-nitrophenol was measured at 405 nm with microplate reader (BioTek, USA). The results expressed as percentage inhibition, were calculated using the following equation:

$$\text{Inhibition (\%)} = [(\text{OD control} - \text{OD sample}) / \text{OD control}] \times 100$$

The IC_{50} value showed the concentration of compound inhibiting 50% of α-glucosidase activity. The IC_{50} value was calculated using TableCurve software.

3. Results and Discussion

The total methanol residue, *n*-hexane extract and chloroform extract from the rhizomes of *Z. zerumbet* were evaluated for α-glucosidase inhibitory activity using acarbose as the positive control. All the three samples exhibited inhibitory effect against α-glucosidase although the chloroform extract showed the most effective activity with IC_{50} value of 126.9 μg/mL, slightly lower than that of acarbose. As for the results, the chloroform extract was chosen for chemical constituent research. By operating repeated CC on silica gel, TLC and crystallization, two compounds 1 (Figure 1) were isolated. The structures of these isolated compounds were elucidated using spectroscopic methods, particularly 1D-NMR spectroscopy, and by comparing with their ^{1}H and/or ^{13}C NMR spectroscopic data with those previously published.

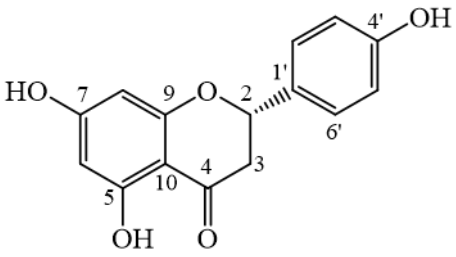

Fig 1: Structures of compounds 1 isolated from *Zingiber zerumbet*.

3.1. Compounds from Z. zerumbet rhizomes

Compound **1** was obtained as pale-yellow powder. The ^{1}H NMR of compound 1 displayed signals for a flavanol with 3 rings A, B and C (C_6-C_3-C_6). Two meta coupling aromatic protons of ring A appeared at δ_H 5.96 (1H, *d*, *J* = 2.2 Hz, H-

8), 5.95 (1H, *d*, *J* = 2.1 Hz, H-6). Signals of four protons of ring B were observed at δ_H 7.39 (2H, *d*, *J* = 8.5 Hz, H-2′, H-6′), 6.90 (2H, *d*, *J* = 8.5 Hz, H-3′, H-5′) suggested signals of a para substituted ring. Signals of ring C including an oxymethine proton at δ_H 5.46 (1H, *dd*, *J* = 12.8, 3.0 Hz, H-2), two nonequivalent ethylene protons at δ_H 3.17 (1H, *dd*, *J* = 17.1, 12.9 Hz, H-3a), 2.73 (1H, *dd*, *J* = 17.1, 3.0 Hz, H-3b). Signals of a chelated hydroxyl proton appeared at δ_H 12.14 (1H, s, 5-OH). The ^{13}CNMR of compound **1** indicated the presence of 15 carbons, including signals of a carbonyl carbon at δ_C 197.2 (C-4), four aromatic carbinols at δ_C 168.5 (C-5), 164.3 (C-9), 165.1 (C-7), 158.6 (C-4'); two non-protonated aromatic carbons at δ_C 130.6 (C-1'), 103.1 (C-10); six aromatic methines at δ_C 129.1 (C-2', C-6'), 116.3 (C-3', C-5'), 96.7 (C-6), 95.8 (C-8); one oxymethine carbon at δ_C 79.8 (C-2] and one aliphatic methylene at δ_C 43.7 (C-3). Above NMR spectra of **1** (Table 1) suggested the existance of a flavone with three hydroxyl group.

Above 1D-NMR spectra analysis established compound **1** to be naringenin. All the NMR data of 1 were identical to those of reported values of naringenin [26].

Table 1: ^{1}H and ^{13}C NMR data of **1** and naringenin [26] (δ ppm, CD_3COCD_3)

	Compound 1 (CD_3COCD_3)		**Naringenin** [26] **(CD_3COCD_3)**	
	δ_H (ppm), *J* (Hz)	**δ_C (ppm)**	**δ_H (ppm), *J* (Hz)**	**δ_C (ppm)**
2	5.46 (1H; *dd*; *J* = 12.8, 3.0)	79.8	5.45 (1H; *dd*; *J* = 12.9, 3.0)	80.0
3a	3.17 (1H; *dd*; *J* = 17.0, 12.9)	43.7	3.17 (1H; *dd*; *J* = 17.1, 12.9)	43.5
3b	2.73 (1H; *dd*; *J* = 17.0, 3.0)		2.74 (1H; *dd*; *J* = 17.1, 3.0)	
4		197.2		197.2
5		168.5		167.8
6	5.95 (1H; *d*; *J* = 2.2)	96.7	5.95 (1H; *d*; *J* = 2.1)	96.4
7		165.1		165.2
8	5.96 (1H; *d*; *J* = 2.2)	95.8	5.96 (1H; *d*; *J* = 2.1)	95.9
9		164.3		164.5
10		103.1		103.2
1'		130.6		130.7
2', 6'	7.39 (2H; *d*; *J* = 8.5)	129.1	7.39 (2H; *d*; *J* = 8.5)	129.0
3', 5'	6.90 (2H; *d*; *J* = 8.5)	116.3	6.90 (2H; *d*; *J* = 8.5)	116.4
4'		158.6		158.7

[a] 500 MHz, [b] 125 MHz, [c] 600 MHz, [d]150 MHz

3.2. α-glucosidase inhibitory activity

The total methanol residue, *n*-hexane extract, chloroform extract and and two isolated compounds from the rhizomes of *Z. zerumbet* were evaluated for *α*-glucosidase inhibitory activity. As shown in Table 2, total methanol residue exhibited weak inhibition against *α*-glucosidase while *n*-hexane extracts did not exhibit inhibitory activity. Chloroform extract showed good inhibitory activity.

Table 2: *α*-glucosidase inhibitory activity of extracts from *Z. zerumbet* rhizomes

Extracts	**Inhibition (I,%)**					**IC_{50} (*μ*g/mL)**
	250 *μ*g/mL	**100 *μ*g/mL**	**50 *μ*g/mL**	**25 *μ*g/mL**	**10 *μ*g/mL**	
Total MeOH residue	88.6 ± 1.5	27.5 ± 2.6	2.3 ± 2.6	–	–	155.2
n-Hexane extract	79.1 ± 2.8	18.6 ± 1.4	–	–	–	177.7
Chloroform extract	94.8 ± 1.5	40.2 ± 2.9	6.4 ± 1.8	–	–	126.9
Acarbose						214.1

*: I > 100%; –: I < 1%

Two compounds isolated from chloroform extract of *Z. zerumbet* rhizomes were evaluated for *α*-glucosidase inhibitory activity. The results are shown in Table 3.

Table 3: *α*-glucosidase inhibitory activity of compounds from *Z. zerumbet* rhizomes

Compound	**Inhibition (I,%)**					**IC_{50} (*μ*M)**
	250 *μ*g/mL	**100 *μ*g/mL**	**50 *μ*g/mL**	**25 *μ*g/mL**	**10 *μ*g/mL**	
Naringenin (1)	*	87.28 ± 0.4	69.83 ± 0.91	58.97 ± 0.68	42.97 ± 0.86	19.6
Acarbose						214.1

*: I > 100%; –: I < 1%

According to the results, compound (1) isolated from chloroform extract of *Z. zerumbet* rhizomes showed promising level of *α*-glucosidase inhibitory activity. The IC_{50} values of naringenin (1) are 19.6 *μ*M, respectively, which are two-fold and eleven-fold lower than that of acarbose (IC_{50} 214.1 *μ*M). The results suggest compound 1 are potential as antidiabetic agents for the inhibition of *α*-glucosidase enzymes.

4. Conclusions

Three extracts and compound (1) form *Z. zerumbet* rhizomes have been investigated for their inhibition activity against *α*-glucosidase. As the results, chloroform extract showed good activity with IC_{50} lower than IC_{50} of acarbose. Compound naringenin (1) isolated from the chloroform extract exhibited strong activity with IC_{50} significantly lower than that of the positive control, particularly naringenin with IC_{50} value of

19.6 μM comparing to 214.1 μM of acarbose. The potential α-glucosidase inhibitory activity of chloroform extract and compounds from *Z. zerumbet* rhizomes providing a theoretical basis for the application of these extracts and compounds in functional foods, medicines or health products in supporting diabete treatment.

Conflicts of Interest: The authors declare no conflict of interest.

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