

## Article

# Zerumbone and Kaempferol Derivatives from the Rhizomes of *Zingiber montanum* (J. Koenig) Link ex A. Dietr. from Bangladesh

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**Abstract:** *Zingiber montanum* (J. Koenig) Link ex A. Dietr. (Zingiberaceae) is known as “Banada” in Bangladesh, and the rhizomes are frequently used in traditional medicines for the treatment of constipation, dyspepsia, flatulence, stomach bloating, and as mosquito repellent. In this study, dried rhizomes were extracted successively with 95% and 50% ethanol and the combined extract was then subjected to various column chromatographic methods to isolate one sesquiterpenoid derivative, zerumbone (1) and five kaempferol derivatives, i.e., kaempferol 3-O-methyl ether (2), kaempferol 3-O- $\alpha$ -rhamnopyranoside (3), kaempferol 3-O- $\alpha$ -(4''-O-acetyl)rhamnopyranoside (4), kaempferol 3-O- $\alpha$ -(3''-O-acetyl)rhamnopyranoside (5), and kaempferol 3-O- $\alpha$ -(3'',4''-di-O-acetyl)rhamnopyranoside (6). All compounds except 1 were isolated for the first time from the title plant.

**Keywords:** *Zingiber montanum*; Zingiberaceae; zerumbone; flavonoids; kaempferol

## 1. Introduction

The Zingiberaceae family has about 50 genera distributed all over the world but mostly in Asia, Central America and Africa. Many plants of Zingiberaceae family are used as food, spice, and medicines [1]. The genus *Zingiber* consists of about 85 species [2] that are used for various purposes as food and medicine. Among them, *Zingiber officinale* Roscoe is the most widely used one. In Bangladesh, eight species of the genus *Zingiber* have been found, namely *Z. capitatum* Roxb., *Z. montanum* (J. Koenig) Link ex A. Dietr., *Z. officinale* Roscoe, *Z. zerumbet* (L.) Roscoe ex Sm., *Z. roseum* Roxb., *Z. rubens* Roxb., *Z. salarkhanii* Rahman et Yusuf. [3], and *Z. spectabile* Griff. [4].

*Zingiber montanum* (J. Koenig) Link ex A. Dietr. (Syns: *Amomum cassumunar* (Roxb.) Donn, *Amomum montanum* J. Koenig, *Amomum xanthorrhiza* Roxb. ex Steud., *Cassumunar roxburghii* Colla, *Jaegera montana* (J. Koenig) Giseke, *Zingiber anthorrhiza* Horan., *Zingiber cassumunar* Roxb., *Zingiber cassumunar* var. *palamauense* Haines, *Zingiber cassumunar* var. *subglabrum* Thwaites, *Zingiber cliffordiae* Andrews, *Zingiber luridum* Salisb., *Zingiber montanum* (J. Koenig ex Retz.) Theilade, *Zingiber purpureum* Roscoe, *Zingiber purpureum* var. *palamauense* (Haines) K.K.Khanna, *Zingiber xanthorrhizon* Steud.) [5] is considered to be native to India and Bangladesh. It is also widely distributed in tropical countries [6] in Southeast Asia and cultivated in Thailand, Malaysia, and Indonesia [7]. In Bangladesh, it is commonly known as “Banada”, meaning wild ginger. The rhizomes of *Z. montanum* are used traditionally to treat constipation, dyspepsia, flatulence, stomach bloating, and as mosquito repellent [8–10]. Previous

pharmacological studies of *Z. montanum* have reported antimicrobial [11], anti-inflammatory [12,13], antioxidant [11], antihistaminic, smooth muscle relaxant [14], antifungal [15], insecticidal activity [16] and anticholinesterase activities [17]. There have been many studies on the volatile constituents of the rhizomes of *Z. montanum* and (*E*)-1-(3,4-dimethoxyphenyl)butadiene, terpinen-4-ol and  $\gamma$ -terpinene [18], 1,4-bis (methoxy) triquinacene, (*Z*)-ocimene, terpinen-4-ol,  $\gamma$ -terpinene, and  $\beta$ -phellandrene [19] were reported as its main constituents. A sesquiterpenoid, zerumbone as an antiulcer compound [8] and the complex curcuminoids, cassumunins A, B, C [12] and cassumunarins A, B, C [20] with potent antioxidant activities were also isolated from the rhizomes.

Various *Zingiber* plants including *Z. montanum* are reported to be used as a substitute and/or adulterant of *Z. officinalis* [21,22]. Recently, *Z. montanum* was also reported as an invasive species in many countries [22]. For the proper utilization of this plant, the detailed chemical analysis of bioactive compounds is necessary. Although there are many studies on volatile constituents of *Z. montanum*, very few studies have reported non-volatile constituents including phenolic compounds. Thus, in this study, we aimed for the isolation and identification of compounds from *Z. montanum* collected from Bangladesh.

## 2. Materials and Methods

### 2.1. General Experimental Procedures

$^1\text{H}$ -,  $^{13}\text{C}$ - and 2D-NMR spectra were measured on an AVANCE 600 NMR spectrometer (Bruker, Billerica, MA, USA) ( $^1\text{H}$ -NMR: 600 MHz and  $^{13}\text{C}$ -NMR: 150 MHz). Chemical shift values ( $\delta_{\text{H}}$  and  $\delta_{\text{C}}$ ) are given in ppm with reference to tetramethylsilane (TMS). Column chromatography was carried out with MCI gel CHP20P (75–150  $\mu\text{m}$ , Mitsubishi Chemical Industries Co. Ltd., Tokyo, Japan), Sephadex LH-20 (Amersham Pharmacia Biotech, Tokyo, Japan), and silica gel 60 (0.040–0.063 mm, Merck KGaA, Darmstadt, Germany). Thin layer chromatography (TLC) was performed on a precoated silica gel 60 F<sub>254</sub> (Aluminum sheet, Merck KGaA, Darmstadt, Germany). Structures of compounds were drawn using the software ChemBioDraw Ultra 14.0 (CambridgeSoft Corporation, PerkinElmer Inc., Cambridge, MA, USA).

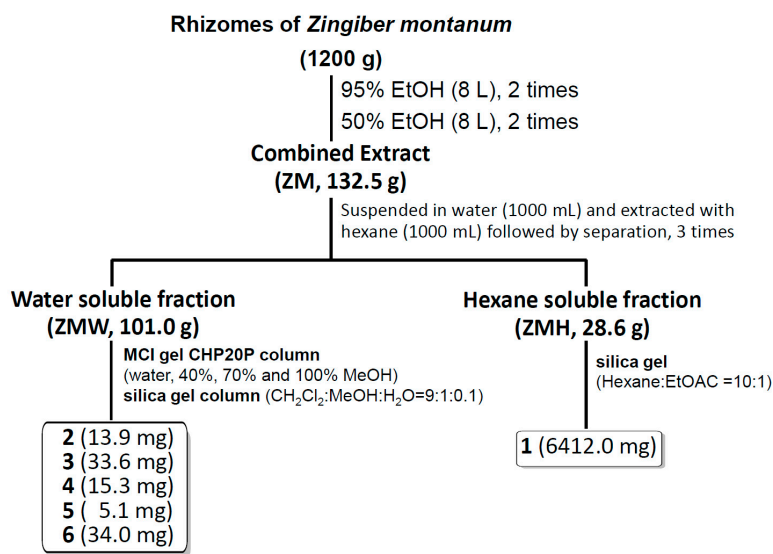
### 2.2. Plant Materials

Fresh rhizomes of *Z. montanum* were collected from Gazipur central area, Gazipur district, Bangladesh in January 2018 and identified by Dr. Mohammad Sayedur Rahman, Senior Scientist, Bangladesh National Herbarium, Dhaka, Bangladesh. A voucher specimen (No. DACB-45749) is deposited at the Museum of Bangladesh National Herbarium.

### 2.3. Extraction and Isolation

Shade dried rhizomes of *Z. montanum* (1200 g) were extracted successively with 95% EtOH and 50% (8 L, two times each for 72 h) at room temperature. The filtered extracts were then combined and evaporated by using a rotary evaporator to obtain 132.5 g of dried extract. The extract was then suspended in water (1000 mL) and extracted with hexane (1000 mL, 3 times) to obtain a hexane fraction and a water-soluble fraction. The hexane fraction (28.6 g) was subjected to silica gel CC (Hex: EtOAc = 10:1) to obtain compound 1 (6412.0 mg). The water-soluble fraction (101.0 g) was subjected to MCI gel CHP20P column chromatography (CC) and eluted successively with water, 40%, 70% and 100% MeOH to give 11 fractions (1–11). Among them, fraction 5 (1.6 g), 6 (1.0 g) and 7 (1.3 g) were mixed and subjected to silica gel CC ( $\text{CH}_2\text{Cl}_2$ : MeOH:  $\text{H}_2\text{O}$  = 9:1:0.1) to afford 6 fractions (Fr. 5-1–5-6). Subfraction 5-2 (1.3 g) was further subjected to silica gel CC ( $\text{CH}_2\text{Cl}_2$ : MeOH:  $\text{H}_2\text{O}$  = 9:1:0.1) to obtain compound 6 (34.0 mg). Subfraction 5-3 (340 mg) was subjected to silica gel CC ( $\text{CH}_2\text{Cl}_2$ : MeOH:  $\text{H}_2\text{O}$  = 9:1:0.1) to obtain compound 5 (5.1 mg). Fraction 5-4 (170 mg) was subjected to silica gel CC ( $\text{CH}_2\text{Cl}_2$ : MeOH:  $\text{H}_2\text{O}$  = 9:1:0.1) to obtain seven subfractions (5-4-1~5-4-7). Subfraction 5-4-2 (65 mg) was again subjected to silica gel CC ( $\text{CH}_2\text{Cl}_2$ : MeOH:  $\text{H}_2\text{O}$  = 9:1:0.1) to obtain compound 4 (15.3 mg).

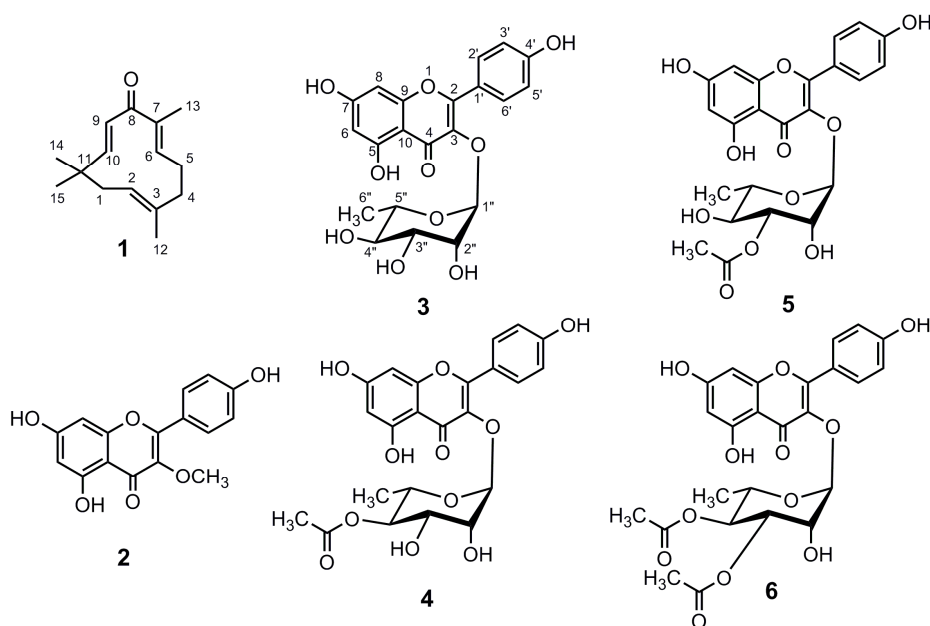
Subfraction 5-4-5 was obtained as compound **3** (33.6 mg). Subfr. 5-5 (100 mg) was subjected to silica gel CC ( $\text{CH}_2\text{Cl}_2$ : MeOH:  $\text{H}_2\text{O}$  = 9:1:0.1) to obtain compound **2** (13.9 mg) (Figure 1).



**Figure 1.** Schematic flowchart of extraction and isolation of compounds from the rhizomes of *Zingiber montanum*.

### 3. Results and Discussion

The detailed chemical analysis of rhizomes of *Z. montanum* afforded a sesquiterpenoid derivative, zerumbone (**1**) [23] and five flavonoid derivatives, kaempferol 3-*O*-methyl ether (**2**) [23], kaempferol 3-*O*- $\alpha$ -rhamnopyranoside (**3**) [24,25], kaempferol 3-*O*- $\alpha$ -(4''-*O*-acetyl) rhamnopyranoside (**4**) [25,26], kaempferol 3-*O*- $\alpha$ -(3''-*O*-acetyl) rhamnopyranoside (**5**) [25] and kaempferol 3-*O*- $\alpha$ -(3'', 4''-di-*O*-acetyl)rhamnopyranoside (**6**) [23] (Figure 2). Compound **6** was obtained as a mixture with compounds **4** and **5**. Structures of these compounds were elucidated on the basis of NMR spectral data (Table 1 for compound **1** and Table 2 for compounds **2**–**6**) and comparison to literature values. To the best of our knowledge, all compounds except **1** were isolated for the first time from *Z. montanum*.



**Figure 2.** Structures of compounds isolated from the rhizomes of *Zingiber montanum*.

**Table 1.** NMR spectroscopic data of compound **1** in CDCl<sub>3</sub>.

Position	δ <sub>C</sub>	δ <sub>H</sub> , mult. (J in Hz)	Position	δ <sub>C</sub>	δ <sub>H</sub> , mult. (J in Hz)
1	42.4	1.89, brd (16.0) 2.22–2.46, m	9	127.2	5.96, d (16.4)
2	125.0	5.25, brd (15.3)	10	160.7	5.86, d (16.4)
3	136.3		11	37.9	
4	39.4	2.22–2.46, m	12	15.2	1.54, s
5	29.4	2.22–2.46, m	13	11.8	1.80, s
6	148.8	6.01, brd (11.3)	14	24.2 <sup>a</sup>	1.20, s <sup>a</sup>
7	138.0		15	24.4 <sup>a</sup>	1.08, s <sup>a</sup>
8	204.3				

<sup>a</sup> Assignments may be interchanged within the same column. Abbreviations: δ<sub>C</sub>: chemical shift in ppm for <sup>13</sup>C-NMR; δ<sub>H</sub>: chemical shift in ppm for <sup>1</sup>H-NMR; mult.: multiplicity; J in Hz: coupling constants in Hz; brd: broad doublet; d: doublet, m: multiplet, s: singlet.

**Table 2.** NMR spectroscopic data of compounds **2–6** in CD<sub>3</sub>OD.

Position	Compound 2		Compound 3		Compound 4		Compound 5		Compound 6	
	δ <sub>C</sub>	δ <sub>H</sub> , mult. (J in Hz)	δ <sub>C</sub>	δ <sub>H</sub> , mult. (J in Hz)	δ <sub>C</sub>	δ <sub>H</sub> , mult. (J in Hz)	δ <sub>C</sub>	δ <sub>H</sub> , mult. (J in Hz)	δ <sub>C</sub>	δ <sub>H</sub> , mult. (J in Hz)
2	157.6		159.2		158.6		159.2		159.2	
3	139.5		136.2		135.6		136.0		135.6	
4	180.1		179.6		179.5		179.6		179.4	
5	163.1		163.2		163.2		163.2		163.2	
6	99.8	6.20, d (2.0)	99.0	6.19, d (2.0)	99.6	6.21, d (2.1)	99.9	6.19, d (2.0)	100.4	6.20, d (2.0)
7	165.9		165.8		165.9		165.9		165.9	
8	94.6	6.40, d (2.0)	94.8	6.36, d (2.0)	94.8	6.38, d (2.1)	94.8	6.38, d (2.0)	94.8	6.52, d (2.0)
9	158.1		158.5		159.4		158.6		158.6	
10	105.7		106.0		105.9		106.0		105.9	
1'	122.2		122.7		122.6		122.6		122.5	
2', 6'	131.4	7.99, d (8.7)	131.9	7.76, d (8.7)	131.9	7.81, d (8.9)	131.9	7.80, d (8.9)	131.8	7.81, d (8.8)
3', 5'	116.4	6.93, d (8.7)	116.5	6.94, d (8.7)	116.5	6.96, d (8.8)	116.6	6.93, d (8.9)	116.6	6.96, d (8.8)
4'	161.7		161.5		161.7		161.6		161.7	
3-OCH <sub>3</sub>	60.4	3.78, s								
1''			103.5	5.38, d (1.5)	102.5	5.51, d (1.5)	103.0	5.50, d (1.3)	102.5	5.59, d (1.3)
2''			72.0	4.22, brs	71.7	4.21, brs	69.7	4.36, brs	72.1	4.34, brs
3''			72.1	3.73, m	70.1	3.84, dd (3.4, 9.8)	75.3	4.97, dd (3.2, 9.8)	69.4	5.16, dd (3.2, 9.8)
4''			73.2	3.31–3.34, m	74.9	4.82, dd (9.8, 9.9)	70.4	3.63, m	71.9	5.07, t (9.8)
5''			71.9	3.31–3.34, m	69.6	3.22, m	71.7	3.40, m	69.4	3.44, m
6''			17.6	0.98, d (5.6)	17.5	0.77, d (6.2)	17.7	0.94, d (6.2)	17.5	0.80, d (6.2)
COCH <sub>3</sub>					172.4		172.7		171.5 172.1	
COCH <sub>3</sub>					20.9	2.03, s	21.1	2.12, s	20.7 20.9	1.97, s 2.06, s

Abbreviations: δ<sub>C</sub>: chemical shift in ppm for <sup>13</sup>C-NMR; δ<sub>H</sub>: chemical shift in ppm for <sup>1</sup>H-NMR; mult.: multiplicity; J in Hz: coupling constants in Hz; brs: broad singlet; d: doublet, dd: double doublet, m: multiple, s: singlet, t: triplet.

Zerumbone (**1**) was isolated in 1960 from *Z. zerumbet* Smith [27] and structurally characterized in 1965 [28]. Other than *Z. zerumbet* [25,29–31], it has also been reported from *Z. montanum* [8], *Z. spectabile* [4] and *Z. aromaticum* [31]. However, it should be noted that Dai et al. [31] reported *Z. zerumbet* and *Z. aromaticum* as separate species collected from the Philippines and Indonesia, respectively but The Plant List [5] currently includes *Z. aromaticum* Valetton as a synonym of *Z. zerumbet* (L.) Roscoe ex Sm. Thus, in the following discussion, the plant source names that authors mentioned in their articles are used irrespective of their current taxonomic classification. There have been extensive studies on zerumbone regarding various biological activities [32], including anti-inflammatory activity

in acute lung injury after lipopolysaccharide (LPS) administration in mice [33], antiparasitic activity in protozoa [34], antioxidant, gastroprotective, antisecretory and anti-*Helicobacter pylori* activities [35], and protection of pancreatic  $\beta$  cell in high glucose induced apoptosis [36]. Similarly, it is reported to be effective in anticancer activity in human breast cancer [37], mouse skin cancer [38] and human cervical cancer cell lines [39]. It is also reported to be effective in protecting ultraviolet B-treated mice from cataractogenesis and photokeratitis [40]. As zerumbone was isolated in a large quantity from *Z. montanum* in our study, it may serve as a suitable source for the isolation of this bioactive compound.

Five kaempferol derivatives (2–6) isolated in this study have been reported to be present in many other plant species of the Zingiberaceae family, and it showed a particularly close resemblance with *Z. zerumbet*. Kaempferol 3-O-methyl ether (2) was isolated previously from the rhizomes of *Z. zerumbet* [25,41,42], *Z. spectabile* [4], *Z. aromaticum* [43], and *Roscoe purpurea* [44], among others. Similarly, kaempferol 3-O- $\alpha$ -rhamnopyranoside (3) was isolated and identified from *Z. ottensii* [45], *Z. aromaticum* [42,43], and *Z. zerumbet* [30]. Kaempferol 3-O- $\alpha$ -(4''-O-acetyl) rhamnopyranoside (5) was isolated from *Z. zerumbet* [30,31,42], *Z. spectabile* [4,46], and *Z. aromaticum* [43]. Kaempferol 3-O- $\alpha$ -(3''-O-acetyl)rhamnopyranoside (5) was isolated from *Z. zerumbet* [25,30,42], *Z. spectabile* [4], *Z. ottensii* [45], and *Z. aromaticum* [43]. Kaempferol 3-O- $\alpha$ -(3'',4''-di-O-acetyl) rhamnopyranoside (6) was isolated from *Z. zerumbet* [23,29,30], *Z. spectabile* [4,46], *Z. ottensii* [45], and *Z. aromaticum* [31,43].

Recently, Jiang et al. [21] reported that *Z. zerumbet* and *Z. montanum* were closely related to *Z. officinale* on the basis of molecular analysis and volatile chemical constituents analysis, respectively. In this study, we observed that the major constituents (zerumbone and flavonoids) isolated from *Z. montanum* were isolated previously from *Z. zerumbet*, which showed its close resemblance with later species. *Z. montanum* may have the potential to be used as an alternative to *Z. zerumbet* as a spice and in medicines. However, further studies are necessary to provide more detailed chemotaxonomic evidences in the future.

#### 4. Conclusions

In conclusion, one sesquiterpenoid derivative, zerumbone (1) and five kaempferol derivatives (2–6) were isolated from the rhizomes of *Z. montanum* collected in Bangladesh. Further studies should be focused on the biological activity analysis of these compounds.

**Author Contributions:** T.I. and H.P.D. conceived and designed the experiments; M.M.H., A.A.-D., and H.P.D. performed the experiments and analyzed the data; M.M.H. and H.P.D. wrote the paper. All authors checked and approved the final version of manuscript.

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**Conflicts of Interest:** Authors declare no conflicts of interest.

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