Sesquiterpenes from *Curcuma zedoaria* rhizomes and their cytotoxicity against human gastric cancer AGS cells

Tae Kyoung Lee[a], Dahae Lee[a], Seoung Rak Lee[a], Yoon-Joo Ko[b], Ki Sung Kang[c], Sang Jeon Chung[a], Ki Hyun Kim[a],*

[a] *School of Pharmacy, Sungkyunkwan University, Suwon 16419, Republic of Korea*
[b] *Laboratory of Nuclear Magnetic Resonance, National Center for Inter-University Research Facilities (NCIRF), Seoul National University, Gwanak-gu, Seoul 08826, Republic of Korea*
[c] *College of Korean Medicine, Gachon University, Seongnam 13120, Republic of Korea*

ABSTRACT

Curcuma zedoaria rhizome (Zingiberaceae) is a well-known traditional medicinal plant used in Ayurvedic and traditional Chinese medicine to treat various cancers. This study aimed to identify the cytotoxic components from *C. zedoaria* rhizomes that act against gastric cancer, which is the third leading cause of death from cancer worldwide because the MeOH extract of *C. zedoaria* rhizome was found to show a cytotoxic effect against gastric cancer AGS cells. Repeated column chromatography and semi-preparative HPLC purification were used to separate the components from the *C. zedoaria* MeOH extract. Two new sesquiterpenes, curcumenol-9,10-epoxide (**1**) and curcuzedoalide B (**2**), and 12 known related sesquiterpenes (**3–14**) were isolated from the *C. zedoaria* MeOH extract. The structures of new compounds were determined by 1D and 2D NMR spectroscopic experiments and HR-ESIMS, and quantum chemical ECD calculations. The cytotoxic effects of the isolated compounds were measured in human gastric cancer AGS cells using an MTT cell viability assay. Compounds **9**, **10**, and **12** exhibited cytotoxic effects against gastric cancer AGS cells, with IC_{50} values in the range of 212–392 μM. These findings provide further experimental scientific evidence to support the traditional use of *C. zedoaria* rhizomes for the treatment of cancer. Curcumenol (**9**), 4,8-dioxo-6β-methoxy-7α,11-epoxycarabrane (**10**), and zedoar-ofuran (**12**) were identified as the main cytotoxic components in *C. zedoaria* rhizomes.

1. Introduction

Cancer is a group of diseases characterized by uncontrolled proliferation and growth of abnormal cells, their invasion into neighboring tissues, and their metastasis to distant organs. It is now the second leading cause of global mortality, estimated to have caused 8.7 million deaths worldwide in 2015 [1,2]. Since potent anticancer activity was observed in alkaloids isolated from *Vinca rosea* Linn in 1959, natural products have been demonstrated to be important sources of plentiful lead compounds for novel anticancer drug discovery [3–6]. Indeed, a number of drugs based on leads isolated from natural products, such as vincristine, paclitaxel, and doxorubicin, are currently used as therapeutic interventions in cancer or are being evaluated in preclinical trials [4–6].

As part of our continuing efforts to discover traditional medicinal plants exhibiting pharmacological potential and to characterize the responsible compounds [7–15], we found that the MeOH extract from rhizomes of *Curcuma zedoaria* Roscoe displayed a cytotoxic effect against gastric cancer AGS cells, which was well matched to the ethnopharmacological evidence of the *C. zedoaria* rhizome as an anticancer agent [16,17]. *C. zedoaria* (Zingiberaceae), also known as white turmeric or zedoaria, is a well-known traditional medicinal plant used in Ayurvedic and traditional Chinese medicine to treat various cancers [16,17]. According to phytochemical studies, *C. zedoaria* rhizome is a rich natural source of sesquiterpenes, which have demonstrated various biological activities including anti-inflammatory [18], cytotoxic [19], and anti-fungal properties [20]. However, the compounds having anticancer activity in the *C. zedoaria* rhizome have not yet been explored in detail. Based on the bioactivity-guided fractionation of the *C. zedoaria* MeOH extract for cytotoxic effects on gastric cancer AGS cells, five sesquiterpenes were isolated from the cytotoxic hexane fraction [21]. Among the isolates, curcuzedoalide was identified as an active compound, which inhibited AGS human gastric cancer cells by activating cleavage of caspases and PARP, which are representative markers for

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apoptosis [21]. These findings led us to further investigate potential cytotoxic components from the *C. zedoaria* rhizome. Additional phytochemical analysis led to the isolation of 14 sesquiterpenes, including two new sesquiterpenes, curcumenol-9,10-epoxide (**1**) and curcuzedoalide B (**2**). Here, we describe the isolation and structural elucidation of these sesquiterpenes (**1–14**) and their cytotoxicity against human gastric cancer AGS cells.

2. Experimental

2.1. General experimental procedures

Optical rotations were calculated on a Jasco P-2000 polarimeter in MeOH (Jasco Inc, Easton, MD, USA). UV spectra were acquired on an Agilent 8453 UV–visible spectrophotometer (Agilent Technologies, Santa Clara, CA, USA). IR spectra were acquired with a Bruker IFS 66/S FT-IR spectrometer (Bruker AXS GmbH, Karlsruhe, Germany). Electronic circular dichroism (ECD) spectra were measured on a Jasco J-1500 spectropolarimeter (Jasco Inc). ESI and HR-ESI mass spectra were recorded using a Waters Micromass Q-Tof Ultima ESI-TOF mass spectrometer (Waters Corporation, Milford, CT, USA). LC/MS analysis was performed using an Agilent 1200 HPLC with a diode array detector system and an analytical Kinetex C18 100 Å column (100 mm × 2.1 mm i.d., 5 μm) (Phenomenex Inc, Torrance, CA) coupled to an Agilent ESI 6130 mass spectrometer. NMR spectra were recorded on a Bruker AVANCE III HD 850 NMR spectrometer with a 5 mm TCI CryoProbe operating at 850 MHz (^{1}H) and 212.5 MHz (^{13}C) (Bruker AXS GmbH), with chemical shifts given in ppm (δ) for ^{1}H and ^{13}C NMR analyses. Preparative HPLC and semi-preparative HPLC were performed with a Waters 1525 binary HPLC pump with a Waters 996 photodiode array detector using an analytical Agilent Eclipse XDB-C18 column (250 × 21.2 mm, 7 μm) (Waters Corporation), a Phenomenex Luna phenyl-hexyl 100 A column (250 × 10 mm, 10 μm) and a Phenomenex Luna C18 100 A column (250 × 10 mm, 10 μm), respectively. Column chromatography was performed with silica gel 60 (Merck KGaC, Darmstadt, Germany; 70–230 mesh and 230–400 mesh) and RP-C$_{18}$ silica gel (Merck, 230–400 mesh). Merck precoated silica gel F$_{254}$ plates and RP-C$_{18}$ F$_{254s}$ plates were used for thin-layer chromatography (TLC). Spots were detected after TLC under UV light or by heating after spraying with anisaldehyde-sulfuric acid. The 3D molecular modeling was performed by using ChemBioDraw Ultra and Avogadro.

2.2. Plant material

The dried rhizomes of *C. zedoaria* were purchased from Kyoungdong Herbal Market, Seoul, in July 2015. The plant material was identified by one of the authors, Ki Hyun Kim. A voucher specimen (BC-2016) was deposited at the herbarium of the School of Pharmacy, Sungkyunkwan University (Suwon, Korea).

2.3. Extraction and isolation

The dried rhizomes of *C. zedoaria* (1.5 kg) were extracted three times with MeOH at 65 °C and filtered. The filtrate was concentrated under reduced pressure using a rotavapor to obtain a crude MeOH extract (69.1 g), which was sequentially solvent partitioned with hexane, CHCl$_3$, EtOAc, and *n*-BuOH to give hexane (19.4 g), CHCl$_3$ (8.6 g), EtOAc (4.1 g), and *n*-BuOH (1.7 g)-soluble fractions. Of these, the hexane and CHCl$_3$ fractions exhibited cytotoxic effects against gastric cancer AGS cells [21]. The hexane-soluble fraction (2.0 g) was further fractionated via silica gel column chromatography using a hexane: EtOAc gradient (from 15:1 to 1:1, v/v) to afford 15 fractions (H1-H15). Fractions H5 (241.1 mg) and H7 (33.0 mg) were separately subjected to semi-preparative HPLC (flow rate: 2 mL/min; Phenomenex Luna C18, 250 × 10.0 mm, 10 μm) using an isocratic solvent system of 70% MeOH, which yielded compounds **3** (t_R 36.5 min, 7.2 mg) and **4** (t_R

42.0 min, 4.0 mg) from fractions H5, and compound **5** (t_R 30.3 min, 0.9 mg) from fractions H7. Fraction H8 (347.0 mg) was further subjected to RP-C$_{18}$ silica gel column chromatography (eluted with 50%→ 75% MeOH, gradient system) to yield 8 subfractions (H81-H88). Subfraction H84 (7.8 mg) was separated by semi-preparative HPLC (60% MeOH) to yield compound **6** (t_R 27.0 min, 1.8 mg). Subfractions H87 (30.5 mg) and H88 (191.3 mg) were consolidated and purified using semi-preparative HPLC (70% MeOH) to furnish compounds **1** (t_R 24.2 min, 2.5 mg), **7** (t_R 27.9 min, 5.1 mg), **8** (t_R 17.0 min, 4.4 mg), and **9** (t_R 21.8 min, 103.6 mg). Fraction H9 (115.5 mg) was separated by semi-preparative HPLC (55% MeOH) to yield compounds **10** (t_R 14.5 min, 2.2 mg) and **11** (t_R 24.3 min, 3.5 mg). Compound **2** (t_R 19.0 min, 2.7 mg) was obtained from fraction H10 (73.0 mg) by semi-preparative HPLC (65% MeOH). Fraction H12 (110.0 mg) was separated by semi-preparative HPLC (60% MeOH) to yield compound **12** (t_R 28.4 min, 3.5 mg). The CHCl$_3$-soluble fraction (0.6 g) was subjected to silica gel column chromatography (60 g, eluted with a CH$_2$Cl$_2$/MeOH [50:1 → 3:1] gradient system) to afford 7 fractions (M1-M7). Fraction M4 (49.2 mg) was separated by semi-preparative C-18 HPLC with 55% MeOH to afford compounds **13** (t_R min, 2.4 mg) and **14** (t_R min, 0.7 mg).

2.3.1. Curcumenol-9,10-epoxide (1)

Colorless gum. [α] + 40.3 (*c* 0.05, MeOH); UV (MeOH) λ$_{max}$ (log ε): 205 (3.6) nm; IR (KBr) ν$_{max}$: 3485, 3356, 2982, 2929, 1709, 1451, 1397, 1116, 972 cm^{-1}; ECD (MeOH) λ$_{max}$ (Δε) 200 (+13.2) nm; ^{1}H NMR (CDCl$_3$, 850 MHz) and ^{13}C NMR (CDCl$_3$, 212.5 MHz) spectroscopic data, see Table 1; HR-ESIMS (positive-ion mode) *m/z*: 251.1624 [M + H]$^+$ (calcd. for C$_{15}$H$_{23}$O$_3$ 251.1647).

2.3.2. Curcuzedoalide B (2)

Colorless gum. [α] + 3.9 (*c* 0.001, MeOH); UV (MeOH) λ$_{max}$ (log ε): 220 (3.6) nm; IR (KBr) ν$_{max}$: 2843, 1705, 1640, 1054, 1032 cm^{-1}; ECD (MeOH) λ$_{max}$ (Δε) 251 (+10.3) nm; ^{1}H NMR (CD$_3$OD, 850 MHz) and ^{13}C NMR (CD$_3$OD, 212.5 MHz) spectroscopic data, see Table 1; HR-ESIMS (positive-ion mode) *m/z*: 273.1469 [M + Na]$^+$ (calcd. for C$_{15}$H$_{22}$O$_3$Na 273.1467)

2.4. Computational analysis

To acquire the conformational optimization of **1a/1b** and **2a/2b**,

Table 1
^{1}H (850 MHz) and ^{13}C NMR (212.5 MHz) data for compounds **1** in CDCl$_3$ and **2** in CD$_3$OD.[a]

Position	1			2		
	δ_H	δ_C		δ_H	δ_C	
1	1.81 s	47.2	d	2.99 dd (11.5, 7.5)	45.2	d
2α	1.81 m	24.6	t	1.29 m	30.4	t
2β	1.63 m					
3α	1.62 m	31.4	t	1.49 m	31.7	t
3β	1.90 m			1.90 m		
4	1.82 m	39.9	d	2.25 m	44.5	d
5		87.0	s		92.1	s
6α	2.10 d (16.0)	36.6	t	2.85 d (16.0)	44.9	t
6β	2.64 d (16.0)			3.00 d (16.0)		
7		131.4	s		213.6	s
8		100.6	s		nd	s
9	3.11 s	60.1	d	5.67 d (1.0)	113.6	d
10		59.4	s		164.2	s
11		128.1	s	2.65 m	43.0	d
12	1.96 s	18.9	q	1.03 d (7.0)	18.0	q
13	1.70 s	22.5	q	1.05 d (7.0)	17.9	q
14	0.98 m	11.5	q	1.98 d (1.0)	22.5	q
15	1.34 s	23.2	q	1.07 d (7.0)	12.0	q

[a] Signal multiplicity and coupling constants (Hz) are in parentheses. The assignments were based on HSQC, HMBC, and ^{1}H – ^{1}H COSY experiments.
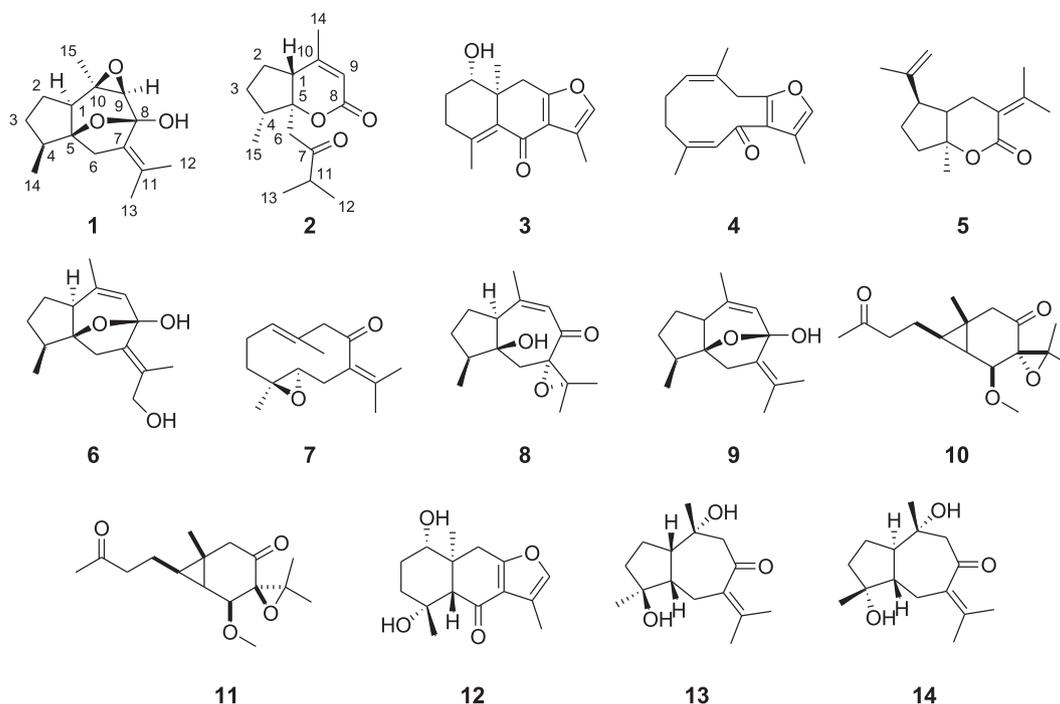
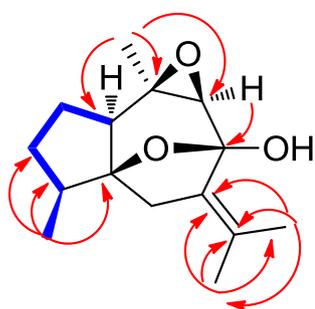**Fig. 1.** Chemical structures of compounds **1–14**.

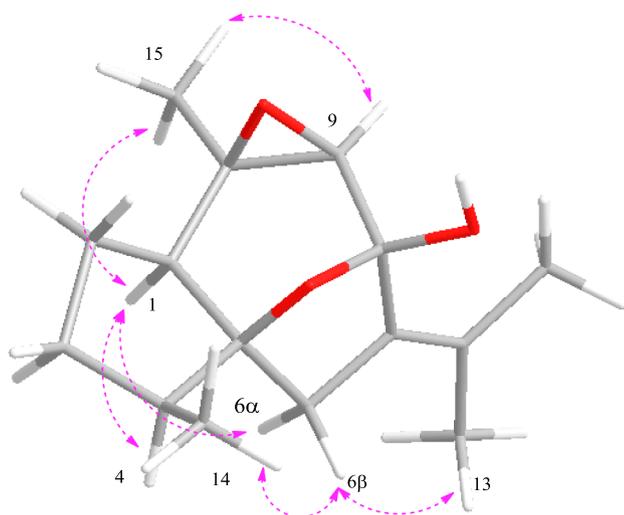**Fig. 2.** $^1H-^1H$ COSY (▬) and key HMBC (⌒) correlations of compound **1**.

Fig. 4. Experimental and calculated ECD spectra of compound **1**.

Fig. 3. The 3D molecular model of compound **1** showing key NOESY (⌒) correlations.

Fig. 5. $^1H-^1H$ COSY (▬) and key HMBC (⌒) correlations of compound **2**.

computational DFT calculations were carried out. The first structural energy minimizations of **1a/1b** and **2a/2b** were performed by utilizing Avogadro 1.2.0 with a UFF force field. The ground-state geometries of
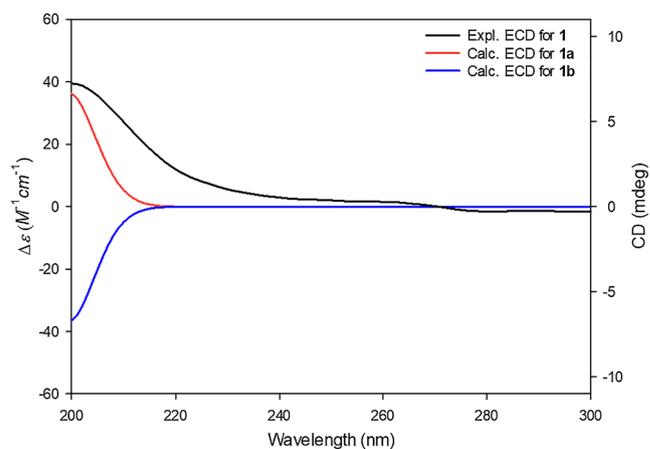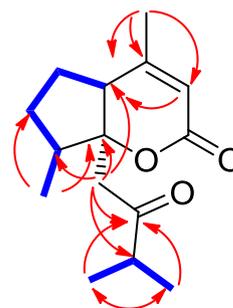
1a/1b and **2a/2b** were then established by TmoleX 4.3.1 with the DFT settings (B3-LYP functional/M3 grid size), geometry optimization options (energy 10^{-6} hartree, gradient norm $|dE/dxyz| = 10^{-3}$ hartree/bohr), and the basis set def-SV(P) for all atoms [22,23]. The calculated ECD spectra of optimized structures were acquired at the B3LYP/DFT functional settings with the basis set def2-TZVPP for all atoms [22,23].
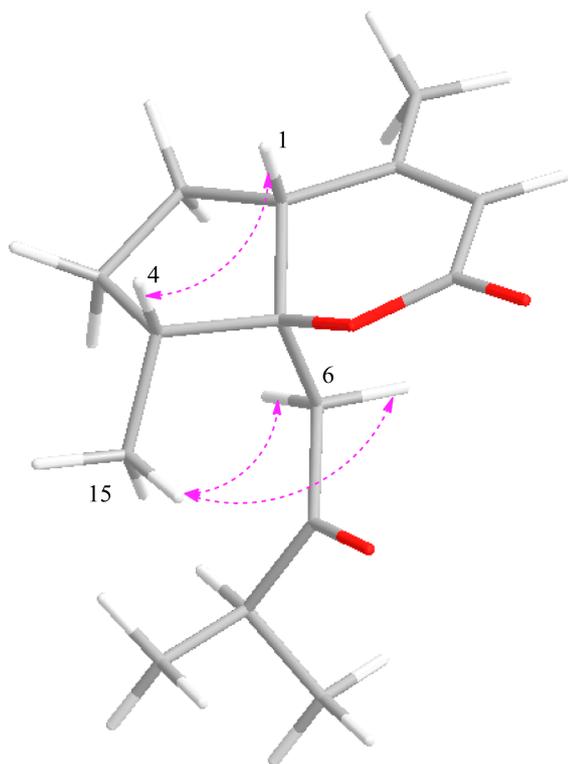
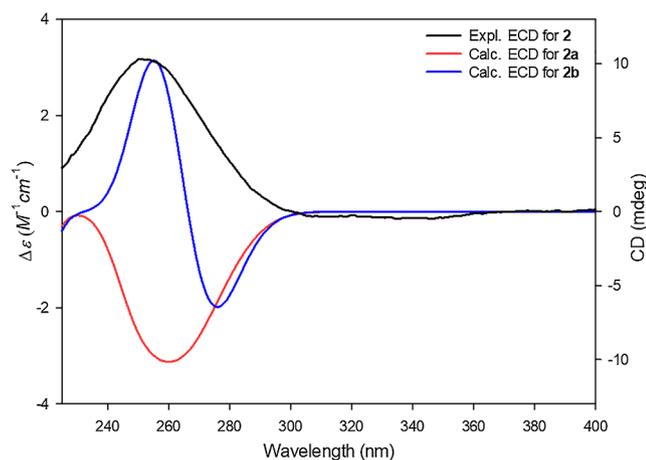**Fig. 6.** The 3D molecular model of compound **2** showing key NOESY (⤺⤻) correlations.

Fig. 7. Experimental and calculated ECD spectra of compound **2**.

The obtained CD spectra were simulated by overlaying each transition, where σ is the width of the band at 1/e height. ΔE_i and R_i are the excitation energies and rotatory strengths for transition i, respectively. In the present study, the value of σ was 0.10 eV.

$$\Delta \epsilon (E) = \frac{1}{2.297 \times 10^{-39}} \frac{1}{\sqrt{2\pi}\sigma} \sum_A^i \Delta E_i R_i e^{[-(E-\Delta E_i)^2/(2\sigma)^2]}$$

2.5. Cell culture

The human gastric cancer AGS cell line was purchased from the American Type Culture Collection (ATCC, Manassas, VA, USA). The cells were cultured in Roswell Park Memorial Institute 1640 medium (Corning, New York, NY, USA) supplemented with 10% fetal bovine serum (Thermo Fisher Scientific, Waltham, MA, USA), 1% sodium pyruvate, 100 units/mL penicillin, and 100 mg/mL streptomycin (Thermo Fisher Scientific) and incubated at 37 °C in a humidified atmosphere with 5% CO_2.

2.6. MTT cell viability assay

AGS cells were seeded at 1×10^4 cells/100 μL in 96-well plates and treated with varying concentrations of the test samples for 24 h. The cells were incubated in cell culture medium with or without samples. After incubation for 24 h, cell viability was determined using the Ez-Cytox cell viability assay kit (Dail Lab Service Co., Seoul, Korea) according to the instructions. Ten microliters of kit reagent was added to each well, and the cells were incubated for 30 min. The absorbance at 450 nm (absorbance for live cells) was measured using a microplate reader (PowerWave XS; BioTek Instruments, Winooski, VT, USA).

3. Results and discussion

3.1. Isolation of compounds from the MeOH extract of C. Zedoaria

The MeOH extract of *C. zedoaria* was solvent partitioned to provide hexane, CHCl₃, EtOAc, and *n*-BuOH-soluble fractions. Among them, the hexane and CHCl₃-soluble fractions inhibited gastric cancer cell viability, with IC₅₀ values of 136.88 ± 2.59 μg/mL and 155.65 ± 1.37 μg/mL, respectively [21]. Based on this result, phytochemical investigation of the hexane and CHCl₃-soluble fractions, combined with LC/MS analysis, using successive column chromatography and HPLC purification resulted in the isolation and identification of 14 sesquiterpenes (**1–14**), including two new sesquiterpenes (**1–2**) (Fig. 1).

3.2. Structural elucidation of the isolated compounds

Compound **1** was obtained as a colorless gum. Its molecular formula was determined to be $C_{15}H_{22}O_3$ based on positive-ion mode HR-ESI-MS data at *m/z* 251.1624 [M + H]⁺ (calcd for $C_{15}H_{23}O_3$, 251.1647) and ¹³C NMR data. Detailed analysis of the NMR data (Table 1) of **1** revealed that the NMR spectra were typical of sesquiterpene and similar to those of curcumenol (**9**) [24]. The major differences in ¹³C NMR data between compound **1** and curcumenol (**9**) were the absence of two sp² carbon signals and the presence of two sp³ signals at δ_C 60.1 and 59.4 in **1** [24]. In the ¹H NMR spectrum of **1** (Table 1), the olefinic proton at δ_H 5.76 for curcumenol (**9**) was replaced by an oxygenated proton at δ_H 3.11 (1H, s), which is correlated to the carbon signal at δ_C 60.1 based on the HSQC spectrum. Analysis of hydrogen deficiency of **1** and the chemical shifts allowed us to deduce the presence of an epoxy group at C-9/C-10 in **1**, instead of the $\Delta^{9,10}$ double bond in curcumenol (**9**) [25]. This deduction was corroborated by the HMBC correlations of CH₃-15 with C-1/C-9/C-10 (Fig. 2) [25,26]. The relative configuration of **1** was established by analysis of NOESY experiments (Fig. 3), where the NOESY correlations from H-1 with H-4/H-6α/CH₃-15, from H-9 with CH₃-15, from CH₃-13 with H-6β, and from CH₃-14 with H-6β indicated α-orientations of H-1 and CH₃-15 and β-orientations of CH₃-14, the epoxy ring, and the oxygen bridge (Fig. 3). In order to confirm the absolute configuration, quantum chemical ECD calculations were performed by the comparison of the experimental ECD spectrum of **1** with the calculated ECD data of two possible enantiomers, **1a** (1*R*,4*S*,5*S*,8*S*,9*R*,10*R*) and **1b** (1*S*,4*R*,5*R*,8*R*,9*S*,10*S*) (Fig. 4). The experimental ECD data of **1** matched well with the calculated ECD curve of **1a**. Thus, the chemical structure of **1** including its absolute configuration (1*R*,4*S*,5*S*,8*S*,9*R*,10*R*) was elucidated as drawn in Fig. 1, and we named compound **1** as curcumenol-9,10-epoxide.

Compound **2** was isolated as a colorless gum. Its molecular formula was determined as $C_{15}H_{22}O_3$ from the positive-ion mode HR-ESI-MS data at *m/z* 273.1469 [M + Na]⁺ (calcd for $C_{15}H_{22}O_3Na$, 273.1467). The ¹H NMR data (Table 1) of **2** showed the signals for four methyl doublets at δ_H 1.03 (3H, d, *J* = 7.0 Hz), 1.05 (3H, d, *J* = 7.0 Hz), 1.07
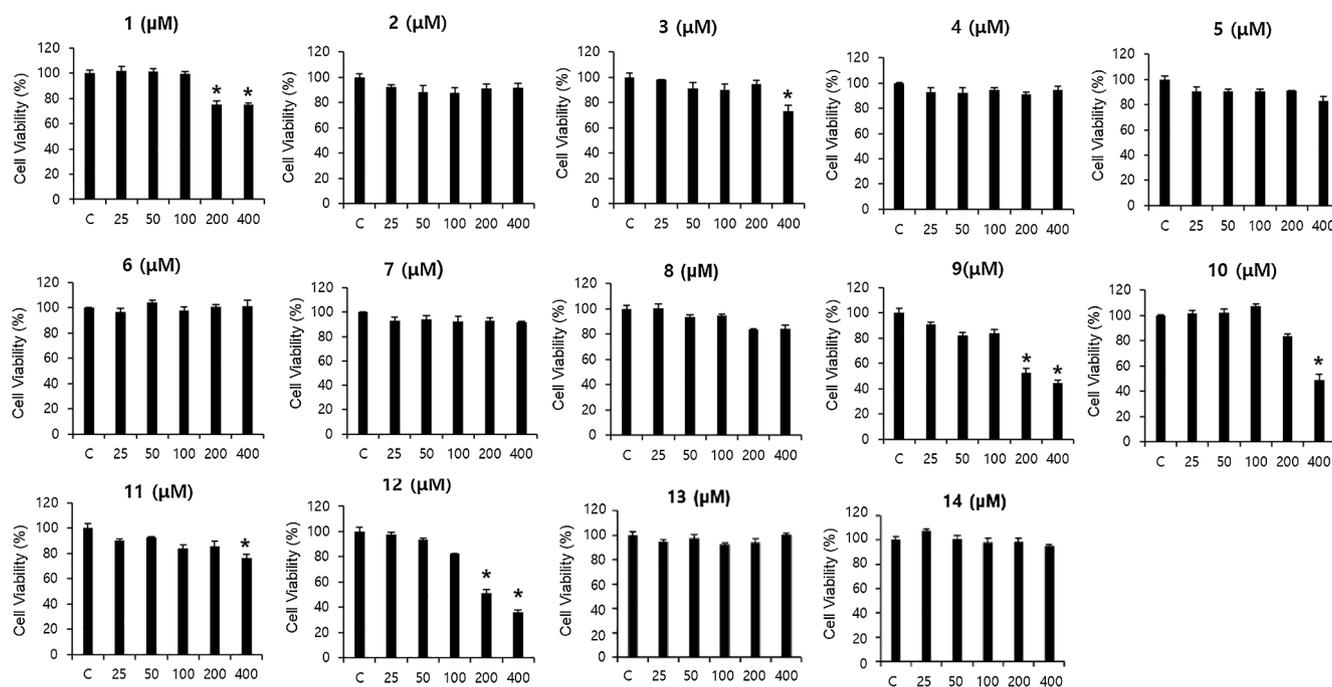
Fig. 8. Effects of isolated compounds **1–14** on AGS human gastric carcinoma cell viability. Cells were treated with the compounds (0, 25, 50, 100, 200, and 400 μM) for 24 h. Relative cell proliferation was measured by the MTT assay. Each value represents the mean $\pm$ SD of three independent experiments. *$p < 0.05$ compared to the not-treated value.

(3H, d, $J = 7.0$ Hz), and 1.98 (3H, d, $J = 1.0$ Hz); methylene proton doublets at δ_H 2.85 (1H, d, $J = 16.0$ Hz) and 3.00 (1H, d, $J = 16.0$ Hz); and one olefinic proton at δ_H 5.67 (1H, d, $J = 1.0$ Hz); and the ^{13}C NMR data (Table 1) indicated the presence of 15 carbon resonances, including a keto-carbonyl, an ester carbonyl, and two olefinic carbons. The NMR data of **2** were almost identical to those of curcuzedoalide, a rare 7,8-seco-guaiane-type sesquiterpene [24,27]. However, the NMR data assigned to the $\Delta^{11,12}$ double bond in curcuzedoalide were absent, and instead, methyl and methine signals were observed in **2**, suggesting the reduction of the $\Delta^{11,12}$ double bond in **2**. This deduction indicated the presence of an isobutyryl group in **2**, which was shown to be linked at C-5 via a methylene bridge by the HMBC correlations of H-6 with C-1/C-4/C-5/C-7/C-11, H-11 with C-7/C-12/C-13, and CH$_3$-12/CH$_3$-13 with C-7/C-11 (Fig. 5). The relative configuration of **2** was confirmed by NOESY experiments (Fig. 6) in which correlations of H-6 with CH$_3$-15 and H-1 with H-4 were observed, indicating that H-6 and CH$_3$-15 had the same orientation and H-1 and H-4 had the opposite (Fig. 6). The absolute configuration of **2** was determined by comparing the calculated and experimental ECD data (Fig. 7), as described for **1**. The experimental ECD curve of **2** was in agreement with the calculated ECD data for **2b** (1*R*,4*R*,5*S*), rather than **2a** (1*S*,4*S*,5*R*) (Fig. 7). Therefore, the structure of **2** was identified as (1*R*,4*R*,5*S*)-7,8-seco-guaia-9(10)-en-8,5-olide, and named curcuzedoalide B. To the best of our knowledge, the (1*S*,4*S*,5*S*)-isomer of **2** was reported from the radix of *Curcuma aromatica* [27].

The other isolated sesquiterpenes from *C. zedoaria* were identified as curcolone (**3**) [28], 1(10)*Z*,4*Z*-furanodiene-6-one (**4**) [29], gajutsu-lactone A (**5**) [30], 12-hydroxycurcumenol (**6**) [31], germacrone-4,5-epoxide (**7**) [24], oxycurcumenol epoxide (**8**) [32], curcumenol (**9**) [24], 4,8-dioxo-6*β*-methoxy-7*α*,11-epoxycarabrane (**10**) [33], 4,8-dioxo-6*β*-methoxy-7*β*,11-epoxycarabrane (**11**) [33], zedoarofuran (**12**) [30], (1*S*,4*S*,5*S*,10*R*)-zedoarondiol (**13**) [34], and wenyujinin R (**14**) [35] by comparison with NMR spectroscopic data from literature and LC/MS analysis. Among the isolates, compounds **4**, **6**, **10** and **11** were isolated and structurally identified from *C. zedoaria* for the first time.

3.3. Cytotoxicity of the isolated compounds against AGS gastric cancer cells

Because the isolated sesquiterpenes originated from the fractions of the *C. zedoaria* MeOH extract showing cytotoxicity against gastric cancer AGS cells, all the isolates were evaluated for *in vitro* cytotoxicity against AGS gastric cancer cells by the MTT cell viability assay [36–39], with cisplatin as the positive control with an IC$_{50}$ value of 68.29 ± 2.70 μM. As shown in Fig. 8, compounds **9**, **10**, and **12** exhibited inhibition of proliferation in a dose-dependent manner in AGS gastric cancer cells with IC$_{50}$ values of **9** (IC$_{50}$: 263.34 ± 2.97 μM), **10** (IC$_{50}$: 392.95 ± 3.19 μM) and **12** (IC$_{50}$: 212.50 ± 2.37 μM), respectively. These findings demonstrated that sesquiterpenes were identified to be the main cytotoxic components in *C. zedoaria* rhizomes.

4. Conclusions

In this study, we provide further experimental scientific evidence to support the traditional use of *C. zedoaria* rhizomes for the treatment of cancer. Phytochemical analysis of the cytotoxic fractions of the *C. zedoaria* MeOH extract led to the isolation of two new sesquiterpenes, namely curcumenol-9,10-epoxide (**1**) and curcuzedoalide B (**2**), and 12 known related sesquiterpenes (**3–14**). Compounds **9**, **10**, and **12** exhibited cytotoxic effects against gastric cancer AGS cells, with IC$_{50}$ values in the range of 212–392 μM. Future studies, including Western blotting analysis, will need to be conducted to confirm the molecular mechanisms of the cytotoxic sesquiterpenes.

Conflicts of interest

The authors declare no competing financial interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.03.015.

References

[1] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (2011) 646–674.

[2] C. Fitzmaurice, C. Allen, R.M. Barber, L. Barregard, Z.A. Bhutta, H. Brenner, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study, JAMA Oncol. 3 (2017) 524-548.

[3] H.F. Ji, X.J. Li, H.Y. Zhang, Natural products and drug discovery. Can thousands of years of ancient medical knowledge lead us to new and powerful drug combinations in the fight against cancer and dementia? EMBO Rep. 10 (2009) 194–200.

[4] J. Mann, Natural products in cancer chemotherapy: past, present and future, Nat. Rev. Cancer 2 (2002) 143–148.

[5] A. Bhanot, R. Sharma, M.N. Noolvi, Natural sources as potential anti-cancer agents: a review, Int. J. Phytomed. 3 (2011) 9–26.

[6] J. Du, X.L. Tang, Natural products against cancer: a comprehensive bibliometric study of the research projects, publications, patents and drugs, J. Cancer Res. Ther. 10 (2014) 27–37.

[7] J.S. Yu, J. Baek, H.B. Park, E. Moon, S.Y. Kim, S.U. Choi, K.H. Kim, A new rearranged eudesmane sesquiterpene and bioactive sesquiterpenes from the twigs of *Lindera glauca* (Sieb. et Zucc.) blume, Arch. Pharm. Res. 39 (2016) 1628–1634.

[8] H.M. So, H.J. Eom, D. Lee, S. Kim, K.S. Kang, I.K. Lee, K.H. Baek, J.Y. Park, K.H. Kim, Bioactivity evaluations of betulin identified from the bark of *Betula platyphylla* var. *japonica* for cancer therapy, Arch. Pharm. Res. 41 (2018) 815–822.

[9] J.S. Yu, H.S. Roh, K.H. Baek, S. Lee, S. Kim, H.M. So, E. Moon, C. Pang, T.S. Jang, K.H. Kim, Bioactivity-guided isolation of ginsenosides from Korean Red Ginseng with cytotoxic activity against human lung adenocarcinoma cells, J. Ginseng Res. 42 (2018) 562–570.

[10] D. Lee, D.S. Lee, K. Jung, G.S. Hwang, H.L. Lee, N. Yamabe, H.J. Lee, D.W. Eom, K.H. Kim, K.S. Kang, Protective effect of ginsenoside Rb1 against tacrolimus-induced nephrotoxicity in renal proximal tubular LLC-PK1 cells, J. Ginseng Res. 42 (2018) 75–80.

[11] D. Lee, K.S. Kang, J.S. Yu, J.Y. Woo, G.S. Hwang, D.W. Eom, S.H. Baek, H.L. Lee, K.H. Kim, N. Yamabe, Protective effect of Korean Red Ginseng against FK-506-induced damage in LLC-PK1 cells, J. Ginseng Res. 41 (2017) 284–289.

[12] S.H. Shin, S.R. Lee, E. Lee, K.H. Kim, S. Byun, Caffeic acid phenethyl ester from the twigs of *Cinnamomum cassia* inhibits malignant cell transformation by inducing c-Fos degradation, J. Nat. Prod. 80 (2017) 2124–2130.

[13] J. Huh, T.K.Q. Ha, K.B. Kang, K.H. Kim, W.K. Oh, J. Kim, S.H. Sung, C-methylated flavonoid glycosides from *Pentarhizidium orientale* rhizomes and their inhibitory effects on the H1N1 influenza virus, J. Nat. Prod. 80 (2017) 2818–2824.

[14] S. Lee, S. Lee, H.S. Roh, S.S. Song, R. Ryoo, C. Pang, K.H. Baek, K.H. Kim, Cytotoxic constituents from the sclerotia of *Poria cocos* against human lung adenocarcinoma cells by inducing mitochondrial apoptosis, Cells 7 (2018) 116.

[15] S. Lee, E. Choi, S.M. Yang, R. Ryoo, E. Moon, S.H. Kim, K.H. Kim, Bioactive compounds from sclerotia extract of *Poria cocos* that control adipocyte and osteoblast differentiation, Bioorg. Chem. 81 (2018) 27–34.

[16] R. Lobo, K.S. Prabhu, A. Shirwaikar, A. Shirwaikar, *Curcuma zedoaria* Rosc. (white turmeric): a review of its chemical, pharmacological and ethnomedicinal properties, J. Pharm. Pharmacol. 61 (2009) 13–21.

[17] S. Lakshmi, G. Padmaja, P. Remani, Antitumour effects of isocurcumenol isolated from *Curcuma zedoaria* rhizomes on human and murine cancer cells, Int. J. Med. Chem. 2011 (2011) 253962.

[18] H. Makabe, N. Maru, A. Kuwabara, T. Kamo, M. Hirota, Anti-inflammatory sesquiterpenes from *Curcuma zedoaria*, Nat. Prod. Res. 20 (2006) 680–685.

[19] W.J. Syu, C.C. Shen, M.J. Don, J.C. Ou, G.H. Lee, C.M. Sun, Cytotoxicity of curcuminoids and some novel compounds from *Curcuma zedoaria*, J. Nat. Prod. 61 (1998) 1531–1534.

[20] Z. Chen, Y. Wei, X. Li, C. Peng, Z. Long, Antifungal activity and mechanism of major compound isolated from hexane extract of *Curcuma zedoaria*, Asian J. Chem. 25 (2013) 6597–6600.

[21] E.B. Jung, T.A. Trinh, T.K. Lee, N. Yamabe, K.S. Kang, J.H. Song, S. Choi, S. Lee, T.S. Jang, K.H. Kim, G.S. Hwang, Curcuzedoalide contributes to the cytotoxicity of *Curcuma zedoaria* rhizomes against human gastric cancer AGS cells through induction of apoptosis, J. Ethnopharmacol. 213 (2018) 48–55.

[22] K.B. Kang, H.W. Kim, J.W. Kim, W.K. Oh, J. Kim, S.H. Sung, Catechin-Bound Ceanothane-Type Triterpenoid Derivatives from the Roots of *Zizyphus jujuba*, J. Nat. Prod. 80 (2017) 1048–1054.

[23] K. Kusakabe, Y. Honmura, S. Uesugi, A. Tonouchi, H. Maeda, K. Kimura, H. Koshino, M. Hashimoto, X. Neomacrophorin, a [4.4.3]Propellane-Type Meroterpenoid from *Trichoderma* sp. 1212-03, J. Nat. Prod. 80 (2017) 1484–1492.

[24] O.A. Hamdi, H. Anouar el, J.A. Shilpi, Z.B. Trabolsy, S.B. Zain, N.S. Zakaria, M. Zulkefeli, J.F. Weber, S.N. Malek, S.N. Rahman, K. Awang, A quantum chemical and statistical study of cytotoxic activity of compounds isolated from *Curcuma zedoaria*, Int. J. Mol. Sci. 16 (2015) 9450–9468.

[25] L.X. Chen, Q. Zhao, M. Zhang, Y.Y. Liang, J.H. Ma, X. Zhang, L.Q. Ding, F. Zhao, F. Qiu, Biotransformation of curcumenol by *Mucor polymorphosporus*, J. Nat. Prod. 78 (2015) 674–680.

[26] G.P. Yin, L.C. Li, Q.Z. Zhang, Y.W. An, J.J. Zhu, Z.M. Wang, G.X. Chou, Z.T. Wang, iNOS inhibitory activity of sesquiterpenoids and a monoterpenoid from the rhizomes of *Curcuma wenyujin*, J. Nat. Prod. 77 (2014) 2161–2169.

[27] S. Dong, C. Li, W. Dai, D. Wang, Y. Qin, M. Zhang, Sesqui- and Diterpenoids from the radix of *Curcuma aromatica*, J. Nat. Prod. 80 (2017) 3093–3102.

[28] J.J. Chen, T.H. Tsai, H.R. Liao, L.C. Chen, Y.H. Kuo, P.J. Sung, C.L. Chen, C.S. Wei, New sesquiterpenoids and anti-platelet aggregation constituents from the rhizomes of *Curcuma zedoaria*, Molecules 21 (2016) E1385.

[29] C.H. Brieskorn, P. Noble, Furanosesquiterpenes from the essential oil of myrrh, Phytochemistry 22 (1983) 1207–1211.

[30] H. Matsuda, T. Morikawa, I. Toguchida, K. Ninomiya, M. Yoshikawa, Medicinal foodstuffs. XXVIII. Inhibitors of nitric oxide production and new sesquiterpenes, zedoarofuran, 4-epicurcumenol, neocurcumenol, gajutsulactones A and B, and zedoarolides A and B, from Zedoariae rhizoma, Chem. Pharm. Bull. 49 (2001) 1558–1566.

[31] A. Saifudin, K. Tanaka, S. Kadota, Y. Tezuka, Sesquiterpenes from the rhizomes of *Curcuma heyneana*, J. Nat. Prod. 76 (2013) 223–229.

[32] K. Firman, T. Kinoshita, A. Itai, U. Sankawa, Terpenoids from *Curcuma heyneana*, Phytochemistry 27 (1988) 3887–3891.

[33] J. Xu, P. Zhang, Z. Ma, Y. Guo, X. Zhao, K. Wei, Two carabrane-type sesquiterpenes from *Vladimiria souliei*, Phytochem. Lett. 2 (2009) 204–206.

[34] Y. Lou, F. Zhao, H. He, K.F. Peng, X.H. Zhou, L.X. Chen, F. Qiu, Guaiane-type sesquiterpenes from *Curcuma wenyujin* and their inhibitory effects on nitric oxide production, J. Asian Nat. Prod. Res. 11 (2009) 737–747.

[35] H.F. Huang, C.J. Zheng, G.Y. Chen, W.Q. Yin, X. Huang, Z.R. Mo, Sesquiterpenoids from *Curcuma wenyujin* dreg and their biological activities, Chin. Chem. Lett. 27 (2016) 1612–1616.

[36] Y. Kim, J. Park, M. Kim, B.Y. Hwang, C. Lee, S. Song, Inhibitory effect of D-chiro-inositol on both growth and recurrence of breast tumor from MDA-MB-231 cancer cells, Nat. Prod. Sci. 23 (2017) 35–39.

[37] C.J. Yao, J.M. Chow, S.E. Chuang, C.L. Chang, M.D. Yan, H.L. Lee, I.C. Lai, P.C. Lin, G.M. Lai, Induction of Forkhead Class box O3a and apoptosis by a standardized ginsenoside formulation, KG-135, is potentiated by autophagy blockade in A549 human lung cancer cells, J. Ginseng Res. 41 (2017) 247–256.

[38] Q.M. Thi Ngo, T.Q. Cao, M.H. Woo, B.S. Min, K.Y. Weon, Cytotoxic triterpenoids from the fruits of *Ligustrum japonicum*, Nat. Prod. Sci. 24 (2018) 93–98.

[39] L.S. Aisyah, Y.F. Yun, T. Herlina, E. Julaeha, A. Zainuddin, I. Nurfarida, A.T. Hidayat, U. Supratman, Y. Shiono, Flavonoid compounds from the leaves of *Kalanchoe prolifera* and their cytotoxic activity against P-388 murine leukimia cells, Nat. Prod. Sci. 23 (2017) 139–145.