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Enhancement of pancreatic lipase inhibitory activity of curcumin by radiolytic transformation

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ABSTRACT

The naturally occurring yellow dietary diarylheptanoid curcumin (**1**) was converted by γ-ray to two new γ-lactones, curculactones A (**2**) and B (**3**), as well as four known transformates, *erythro*-1-(3-methoxy-4-hydroxy-phenyl)-propan-1,2-diol (**4**), *threo*-1-(3-methoxy-4-hydroxy-phenyl)-propan-1,2-diol (**5**), vanillic acid (**6**), and vanillin (**7**). The structures of the two new γ-lactone derivatives were elucidated on the basis of spectroscopic methods. The steroisomeric phenylpropanoids **4** and **5** exhibited significantly enhanced inhibitory activity against pancreatic lipase when compared to parent curcumin.

Curcumin is the main yellow bioactive constituent isolated from *Curcuma longa*. It has been shown to possess a wide spectrum of biological properties such as anti-inflammatory, anti-carcinogenic, anti-mutagenic, anti-coagulant, anti-diabetic, and antioxidant activities.[1] Recent studies have demonstrated that some demethoxy derivatives of curcumin also exhibit promising cancer chemopreventive and antioxidative effects as well as effects on cancer cell lines.[2–4] However, curcumin is unstable under neutral and basic pH conditions due to a highly reactive β-diketone moiety and has limited clinical efficacy due to its low bioavailability under physiological conditions.[5,6] Therefore, many studies have been attempted for the structural modification of curcumin to enhance its bioactivities and bioavailability.[7–9]

Obesity is caused by an imbalance between energy intake and expenditure and is widely recognized as a major public health problem. Obesity can result in hypertension, hyperlipidemia, arteriosclerosis, and type II diabetes.[10] Pancreatic lipase is a key enzyme for triglyceride absorption in the small intestine. This enzyme is secreted from the pancreas and hydrolyzes triglycerides into glycerol and fatty acids.[11] Therefore, pancreatic lipase inhibitors are considered to be a valuable therapeutic reagent for treating diet-induced obesity in humans. The success of orlistat,[12] which is a specific pancreatic lipase inhibitor, has prompted research to identify new enzyme inhibitors derived from several medicinal plants.[13]

Recently, several papers have demonstrated that γ-irradiation has potential in modifying flavonoids to have higher bioactivity.[14] However, research relating to radiolytic transformation of naturally occurring compounds is still very limited. As part of our continuing search for novel bioactive compounds, we herein report the radiolytic transformation of curcumin into new γ-lactones as well as related derivatives that exhibited significantly improved pancreatic lipase inhibitory activity than that of their parent compound.

Methanol solution containing curcumin (**1**) was subjected to radiolytic transformation[15] by γ-irradiation, and their degraded products were detected by HPLC analysis. Chromatographic separation[16] yielded two new compounds, curculactone A (**2**) and curculactone B (**3**), along with previously known *erythro*-1-(3-methoxy-4-hydroxy-phenyl)-propan-1,2-diol (**4**),[17] *threo*-1-(3-methoxy-4-hydroxy-phenyl)-propan-1,2-diol (**5**),[18] vanillic acid (**6**),[19] and vanillin (**7**). The known compounds were identified by comparison of their physicochemical and spectroscopic data with those of authentic samples and literature values (Fig. 1).

Compound **2** was obtained as a colorless oil, $[\alpha]_D^{20}$ −7.0° (MeOH). The characteristic absorbances at 229 and 281 nm in the UV spectrum suggested the presence of an aromatic group. The molecular formula $C_{12}H_{14}O_4$ for **2** was determined from an ion peak at *m/z* 222.0890 $[M]^+$ in the HREIMS and NMR data described below. The ^1H NMR spectrum of **2** (Table 1) showed ABX-type aromatic signals at δ_H 6.81 (1H, d, J = 8.4 Hz, H-5′), 6.77 (1H, d, J = 1.8 Hz,

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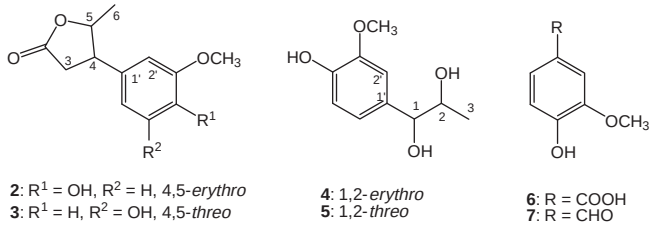

Figure 1. Structures of radiolytic degradation products **2**–**7** of curcumin.

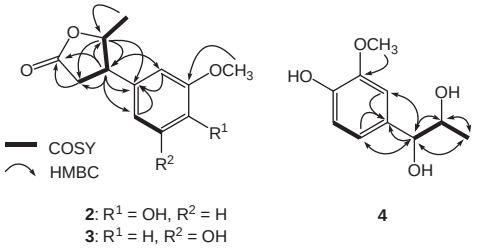

Figure 2. Selected COSY and key HMBC correlations of **2**–**4**.

Table 1
^{1}H and ^{13}C NMR chemical shifts of compounds **2** and **3**[a]

Position	**2**		**3**	
	δ_H[b] (J in Hz)	δ_C, mult.	δ_H[b] (J in Hz)	δ_C, mult.
2	—	179.8	—	178.5
3α	3.00 (dd, 17.4, 8.4)	35.9	2.90 (dd, 9.6, 1.2)	38.5
3β	2.84 (dd, 17.4, 6.0)			
4	3.79 (dd, 14.4, 6.0)	45.7	3.22 (m)	50.7
5	4.98 (quint, 6.0)	82.2	4.57 (dd, 9.6, 6.0)	85.1
6	1.04 (d, 6.6)	16.8	1.41 (d, 6.0)	19.1
1′	—	130.8	—	131.2
2′	6.77 (d, 1.8)	112.8	6.96 (s)	112.1
3′	—	149.1	—	149.4
4′	—	147.1	6.81 (s)	116.5
5′	6.81 (d, 8.4)	116.4	—	147.2
6′	6.66 (dd, 8.4, 1.8)	121.4	6.81 (s)	121.1
OCH_3	3.88 (s)	56.5	3.90 (s)	56.5

[a] ^{1}H NMR measured at 600 MHz, ^{13}C NMR measured at 150 MHz; obtained in CD_3OD with TMS as internal standard. Assignments based on HMQC and HMBC NMR spectra.
[b] J values (Hz) are given in parentheses.

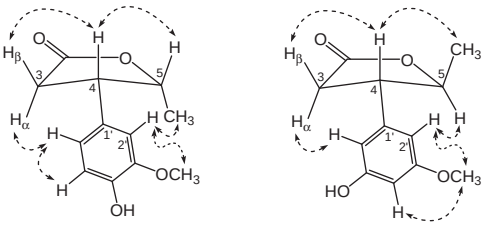

Figure 3. Selected NOESY correlations of **2** and **3**.

H-2′), and 6.66 (1H, dd, J = 8.4, 1.8 Hz, H-6′), indicating the presence of a 1,3,4-trisubstituted benzene ring in **2**. The presence of a γ-lactone moiety was also revealed in the ^{1}H NMR spectrum in the well-defined aliphatic region, which shows signals from one oxygenated methine proton at δ_H 4.98 (1H, quint, J = 6.0 Hz, H-5), one benzylic methine proton at δ_H 3.79 (1H, dd, J = 14.4, 6.0 Hz, H-4), one methylene group at δ_H 3.00 (1H, dd, J = 17.4, 8.4 Hz, H-3α), 2.84 (1H, dd, J = 17.4, 6.0 Hz, H-3β), one methyl group at δ_H 1.04 (3H, d, J = 6.6 Hz, H-6), and one methoxyl group at δ_H 3.88 (3H, s). This partial structure was supported by the appearance of ^{13}C NMR resonances (Table 1), which were further supported by cross peaks of H-4/H-3, -5,and H-5/H-6 in the ^{1}H–1H COSY as well as long-range correlations of H-4/C-1′, -2, -2′, -3, -5, -6, -6′, H-5/C-1′, 3, -4, -6, and CH_3-6/C-4, -5 in the HMBC spectrum. The position of the methoxyl group was confirmed unambiguously by HMBC (OCH_3/C-3′) and NOESY (OCH_3/H-2′) experiments (Figs. 2 and 3).

Comparison of the ^{1}H and ^{13}C NMR spectra of **2** with previously known descurainolide A[20] readily identified that this new compound possesses the same structure, except for the absence of a methoxyl group at the C-3′ position. The relative stereostructures of the 4 and 5-positions in the γ-lactone moiety were characterized by NOESY spectrum (Fig. 3). The spectrum of **3** displayed correlations between H-2′/H-6 (CH_3), H-4/H-5, 3β, and H-6′/H-3α, indicating an *erythro* relationship between the phenyl moiety and the methyl group. Thus, the structure of curculactone A (2)[21] was assigned as shown.

The HREIMS of compound **3**, $[\alpha]_D^{20}$ −24.5° (MeOH), showed a pseudomolecular ion peak at m/z 222.0891 $[M]^+$, indicating that the molecular formula ($C_{12}H_{14}O_4$) was the same as that of **2**. Most of the NMR signals in **3** were nearly identical to those of **2**, except for the different AB_2 splitting patterns[22] of the aromatic signals at δ_H 6.96 (1H, s) and 6.81 (2H, s) in **3**. These proton signals along with the corresponding carbon resonances assigned by 2D NMR techniques showed the presence of a unique skeleton[20] with the same molecular formula as in **2**. The relative configuration of **3** was also determined by NOESY correlations of H-2′/H-5′, H-4/H-6 (CH_3), 3β, and H-6′/H-3α. Consequently, the structure of compound **3** was assigned to curculactone B,[23] which is unknown in the literature.

Compound **4** was obtained as a colorless oil, $[\alpha]_D^{20}$ −10.0° (MeOH). The HRESMS of **4** had a molecular ion peak at m/z 198.0889 $[M]^+$, which is consistent with the molecular formula $C_{10}H_{14}O_4$. The 1D ^{1}H NMR and ^{1}H–1H COSY spectra of **4** indicated the presence of aromatic protons at δ_H 6.97 (1H, d, J = 1.8 Hz, H-2′), 6.77 (1H, dd, J = 7.8, 1.8 Hz, H-6′), and 6.73 (1H, dd, J = 7.8 Hz, H-6′), as well as two oxymethine protons at δ_H 4.38 (1H, d, J = 5.4 Hz, H-1) and 3.82 (1H, dq, J = 6.6, 5.4 Hz, H-2), a methyl proton at δ_H 1.11 (3H, d, J = 6.6 Hz, H-3), and a methoxyl group at δ_H 3.84 (3H, s). In addition to the methoxyl carbon signal, nine skeletal carbon signals appeared in the ^{13}C NMR spectrum. These spectral features suggest that **4** was a penylpropanoid with two hydroxyl groups in its propane moiety.[24] The methoxyl group was located at C-3′, based on the HMBC and NOESY (δ_H 3.84/H-2′) correlations (Figs. 2 and 3). The *erythro* relationship[25] between H-1 and H-2 was inferred from their coupling constant ($J_{1,2}$ = 5.4 Hz) and verified by key NOESY correlations between H-1 and H-2, 2′. Compound **4** was previously reported as a synthetic compound[17] without assigning the NMR data. Thus, compound **4** was assigned to *erythro*-1-(3-methoxy-4-hydroxy-phenyl)-propan-1,2-diol.[26]

The compounds isolated from irradiated curcumin solution were evaluated for their ability to inhibit pancreatic lipase activity[27] using orlistat as a positive control (Table 2). Among the tested compounds, some derivatives possessed significantly higher pancreatic lipase inhibitory activity than that of their parent curcumin (**1**). Two phenylpropanoid-type byproducts, *erythro*-1-(3-methoxy-4-hydroxy-phenyl)-propan-1,2-diol (**4**) and *threo*-1-(3-methoxy-4-hydroxy-phenyl)-propan-1,2-diol (**5**), exhibited the most potent pancreatic lipase inhibitory activities in a dose-dependent manner with IC_{50} values of 9.1 ± 0.2 and 12.1 ± 0.3 μM, respectively. On the other hand, the unusual γ-lactone derivatives curculactones A (**2**) and B (**3**) displayed lower inhibitory effects than those of **4** and **5** with IC_{50} values of 231.5 ± 2.9 and 65.3 ± 2.2 μM, respectively. These results suggest that the stereochemistry at the γ-lactone moiety may have influenced pancreatic

Table 2
Pancreatic lipase inhibitory activity of compounds **1**–**7**

Compound	IC_{50} value (μM)
1	>250
2	231.5 ± 2.9
3	65.3 ± 2.2
4	12.1 ± 0.3
5	9.1 ± 0.2
6	>250
7	74.4 ± 2.1
Orlistat[a]	0.6 ± 0.2

[a] Used as positive control.

lipase inhibition. Two simpler phenolic compounds among the obtained compounds, vanillic acid (**6**) and vanillin (**7**), did not show significantly improved inhibitory activity when compared to the other tested compounds. During the last decade, synthetic modification of curcumin to enhance its bioactivity has been performed.[28,29] Apart from the previously reported biological improvement of modified curcumin, this is the first report on the isolation and evaluation of the biological activities of curcumin byproducts produced by radiolytic degradation using γ-ray.

The results of this study established that curcumin (**1**) was converted into small amounts of two new compounds, curculactones A (**2**) and B (**3**), as well as four previously known compounds, *erythro*-1-(3-methoxy-4-hydroxy-phenyl)-propan-1,2-diol (**4**), *threo*-1-(3-methoxy-4-hydroxy-phenyl)-propan-1,2-diol (**5**), vanillic acid (**6**), and vanillin (**7**) by γ-irradiation. Their structures, including four stereochemically pure compounds (**2**–**5**), were established on the basis of spectroscopic data interpretation. Compounds **2**–**5** were evaluated for their inhibitory activities against pancreatic lipase, and compounds **3** and **4** were the most potent molecules with much lower IC_{50} values than that of original curcumin or the other products tested. In addition, it can be concluded that γ-irradiation of curcumin may be a favorable method for modifying structure and enhancing bioactivity. Further isolation and biological evaluation of non-phenolic constituents are currently in progress.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.12.122.

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15. Irradiation was carried out at ambient temperature, using a cobalt-60 irradiator (point source AECL, IR-79, MDS Nordion International Co. Ltd, Ottawa, ON, Canada) in the Advanced Radiation Technology Institute, Korea Atomic Energy Research Institute (Jeongup, Korea). The source strength was approximately 320 kCi, with dose rate at the location of the sample of 10 kGy/h. Dosimetry was performed using 5 mm diameter alanine dosimeters (Bruker Instruments, Rheinstetten, Germany). The dosimeters were calibrated against an International Standard Set by the International Atomic Energy Agency (Vienna, Austria). Sample solution (2 g curcumin in 200 mL MeOH) in chapped vials were irradiated with 30 kGy (absorbed dose). The irradiated methanolic solution was immediately evaporated to remove the solvent and lyophilized.
16. The dried methanolic solution was directly subjected to column chromatography over a YMC GEL ODS AQ 120-50S column (1.1 cm i.d. × 37 cm) with aqueous MeOH, to yield pure compounds **2** (1.8 mg, t_R 16.3 min), **3** (4.3 mg, t_R 20.5 min), **4** (2.2 mg, t_R 2.9 min), **5** (1.6 mg, t_R 3.4 min), **6** (1.5 mg, t_R 6.9 min), and **7** (3.6 mg, t_R 8.7 min). HPLC analysis was carried out on a YMC-Pack ODS A-302 column (4.6 mm i.d. × 150 mm; YMC Co., Ltd) and was developed at 40 °C with 10 mM H_3PO_4/10 mM KH_2PO_4/MeCN (4.3:4.3:1.4, flow rate: 1.0/min, detection: 280 nm).
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21. *Curculactone A* (**2**): colorless oil, $[\alpha]_D^{20}$ −7.0° (*c* 0.5, MeOH); UV λ_{max} MeOH nm (log ε): 229 (3.71), 281 (1.70); ^1H and ^{13}C NMR, see Table 1; EIMS *m*/*z* 222 $[M]^+$, HREIMS *m*/*z* 222.0890 $[M]^+$ (calcd for $C_{12}H_{14}O_4$, 222.0892).
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23. *Curculactone B* (**3**): colorless oil, $[\alpha]_D^{20}$ −24.5° (*c* 0.2, MeOH); UV λ_{max} MeOH nm (log ε): 229 (3.73), 281 (1.72); ^1H and ^{13}C NMR, see Table 1; EIMS *m*/*z* 222 $[M]^+$, HREIMS *m*/*z* 222.0891 $[M]^+$ (calcd for $C_{12}H_{14}O_4$, 222.0892).
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26. *Erythro-1-(3-methoxy-4-hydroxy-phenyl)-propan-1,2-diol* (**4**): colorless oil, $[\alpha]_D^{20}$ −10.0° (*c* 0.1, MeOH); UV λ_{max} MeOH nm (log ε): 229 (3.00), 280 (1.35); ^1H NMR (CD_3OD, 600 MHz): δ_H 6.97 (1H, d, *J* = 1.8 Hz, H-2′), 6.77 (1H, dd, *J* = 7.8, 1.8 Hz, H-6′), 6.73 (1H, d, *J* = 7.8 Hz, H-5′), 4.38 (1H, d, *J* = 5.4 Hz, H-1), 3.84 (3H, s, MeO-3′), 3.82 (1H, dq, *J* = 6.6, 5.4 Hz, H-2), 1.11 (3H, d, *J* = 6.6 Hz, H-3); ^{13}C NMR (CD_3OD, 150 MHz): 148.7 (C-3′), 146.8 (C-4′), 134.8 (C-1′), 120.9 (C-6′), 115.6 (C-5′), 111.6 (C-2′), 79.0 (C-1), 72.4 (C-2), 59.3 (C-3′ MeO), 18.5 (C-3); EIMS *m*/*z* 198 $[M]^+$, HREIMS *m*/*z* 198.0893 $[M]^+$ (calcd for $C_{10}H_{14}O_4$, 198.0892).
27. *Assay of pancreatic lipase activity*: The ability of the compounds to inhibit porcine pancreatic lipase was evaluated using the previously reported method with a minor modification (Kim, J. H.; Kim, H. J.; Park, H. W.; Youn, S. H.; Choi, D. Y.; Shin, C. S. *FEMS Microbiol. Lett.* **2007**, *276*, 93.). Briefly, an enzyme buffer was prepared by the addition of 30 μL (10 units) of a solution of porcine pancreatic lipase (Sigma, St. Louis, MO) in 10 mM MOPS (morpholine-propanesulphonic acid) and 1 mM EDTA, pH 6.8] to 850 μL of Tris buffer (100 mM Tris–HC1 and 5 mM $CaCl_2$, pH 7.0). Then, 100 μL of the compounds at the test concentration or orlistat (Roche, Basel, Switzerland) was mixed with 880 μL of the enzyme-buffer, and incubated for 15 min at 37 °C, with 20 μL of the substrate solution [10 mM *p*-NPB (*p*-nitrophenylbutyrate) in dimethyl formamide] added and the enzymatic reactions allowed to proceed for 15 min at 37 °C. The pancreatic lipase activity was determined by measuring the hydrolysis of *p*-NPB to *p*-nitrophenol at 405 nm using an ELISA reader (Tecan, Infinite F200, Austria). Inhibition of the lipase activity was expressed as the percentage decrease in the OD when porcine pancreatic lipase was incubated with the test compounds.
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