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Highly oxygenated and unsaturated metabolites providing a diversity of hispidin class antioxidants in the medicinal mushrooms *Inonotus* and *Phellinus*

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Abstract—Three new highly oxygenated and unsaturated metabolites named interfungins A (**1**), B (**2**), and C (**3**), which provide a diversity of hispidin class compounds in the fungi *Inonotus* and *Phellinus*, were isolated from the methanolic extract of the fruiting body of the fungus *Inonotus xeranticus* (Hymenochaetaceae). Their structures were established by spectroscopic methods. The existence of these functionalized metabolites implies that inoscavin A, davallialactone, and phelligridin F, which were previously isolated from the fungi *Inonotus* and *Phellinus* spp., are derived from **1**. Compound **1** is derived from the condensation of hispidin and hispolon. Inoscavins B and C previously isolated from the fungus *I. xeranticus* are most probably derived from **2** which stemmed from the oxidative coupling of 3,4-dihydroxybenzalacetone and hispidin. This class of compounds exhibited significant free radical scavenging activity against the superoxide radical cation, ABTS radical anion, and DPPH radical.

1. Introduction

Mushrooms are nutritionally functional foods and important sources of physiologically beneficial medicines. They produce various classes of secondary metabolites with interesting biological activities and, thus, have the potential to be used as valuable chemical resources for drug discovery.[1,2] Several mushrooms belonging to the genera *Inonotus* and *Phellinus*, such as *Inonotus obliquua*, *Phellinus linteus*, *Phellinus ribis*, and *Phellinus igniarius*, have been used as traditional medicines for the treatment of gastrointestinal cancer, cardiovascular disease, tuberculosis, liver or heart diseases, fester, bellyache, bloody gonorrhea, stomach ailments, and diabetes.[3–5] Polysaccharides, especially β-glucan, are considered to be responsible for their biological activity and there are many reports in the literature on the isolation and biological activity of polysaccharides derived from medicinal mushrooms.[6–8]

Interestingly, these mushrooms commonly produce a bundle of yellow antioxidant pigments that is composed of hispidin derivatives and polyphenols. In previous investigations, inoscavins A–C, phelligridins A–G, phelligridimer A, and polyphenolic compounds were isolated from the fruiting bodies of *Inonotus* and *Phellinus* species.[9–13] In our ongoing efforts to characterize the antioxidant constituents from medicinal mushrooms, we have isolated three new highly functionalized metabolites named interfungins A (**1**), B (**2**), and C (**3**), (Fig. 1) from the fruiting bodies of the fungus *Inonotus xeranticus* (Berk.) Imaz. Et Aoshi. (Hymenochaetaceae), which is a saprophytic fungus living preferentially on deciduous trees such as *Quercus*. These metabolites are the source of a diversity of hispidin-derived compounds with unprecedented carbon skeletons. In this paper, the isolation, structure determination, and antioxidant activity of **1**–**3** are described and the biogenetic pathway by which the different hispidin analogues are derived is discussed.

2. Structures of interfungins A–C

The fresh fruiting bodies of the fungus *I. xeranticus* were extracted twice with MeOH. The methanolic extract was partitioned between *n*-hexane and H_2O, and then

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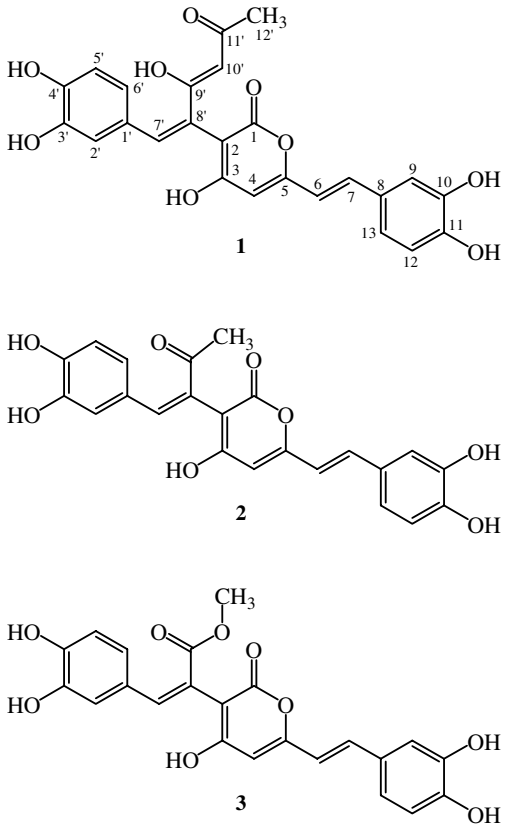


Figure 1. Structures of compounds **1**–**3**.

between ethyl acetate and H_2O. Repeated chromatographic separations of the ethyl acetate-soluble fraction led to the purification of three yellow antioxidant substances **1**–**3**.

The molecular weight of compound **1** was determined to be 464 daltons by the ESIMS measurement, which exhibits quasi-molecular ion peaks at *m/z* 487 $[M+Na]^+$ in the positive mode and *m/z* 463 $[M-H]^-$ in the negative mode. The molecular formula, $C_{25}H_{20}O_9$, was deduced from the HRESIMS ion peak at *m/z* 465.1200 $[M+H]^+$ (calcd for $C_{25}H_{21}O_9$, 465.1180). This molecular formula requires 16 degrees of unsaturation. The absorptions in the IR spectrum of compound **1** suggested the presence of hydroxyl (3421 cm^{-1}), conjugated carbonyl (1654 cm^{-1}), and aromatic (1599 and 1550 cm^{-1}) moieties. The UV absorption bands at λ_{max} (MeOH)(log ε) 215 (4.24), 254 (4.04), and 377 (4.25) nm suggested that **1** has a hispidin moiety.[9,12] The ^1H NMR spectrum in CD_3OD showed six aromatic methine signals assignable to two AMX spin systems of 1,2,4-trisubstituted aromatic systems at δ 7.06 (1H, d, J = 2.0 Hz), 6.98 (1H, dd, J = 8.0, 2.0 Hz), and 6.79 (1H, d, J = 8.0 Hz), and δ 6.94 (1H, d, J = 2.0 Hz), 6.84 (1H, dd, J = 8.4, 2.0 Hz), and 6.70 (1H, d, J = 8.4 Hz), two singlets of sp^2 methine protons at δ 7.73 and 6.20, pair of vinylic protons of *trans* disubstituted double bond at δ 7.37 (1H, d, J = 16.0 Hz) and 6.65 (1H, d, J = 16.0 Hz), and a methyl singlet at δ 2.06. In the ^1H NMR spectrum measured in acetone-d_6, an olefinic methine proton at δ 5.81 and a hydrogen-bonded hydroxyl proton at δ 16.4 in addition to proton signals observed in CD_3OD were evident. The hydrogen-bonded hydroxyl proton revealed *cis* geometry between C-9′ and C-10′. The ^{13}C NMR spectrum in CD_3OD revealed the presence of 24 carbons comprised of one methyl, ten sp^2 methines, and thirteen quaternary carbons including a ketone and ester carbonyls and seven oxygenated sp^2 carbons. The carbon peak at δ 98.0 (C-10′), which was assigned by the HMBC cross-peak from the methyl protons at δ 2.06, was not detectable in the ^{13}C NMR spectrum in CD_3OD. The above spectroscopic data suggested that **1** was a highly oxygenated and unsaturated aromatic compound. The proton-bearing carbons were assigned with the aid of the HMQC spectrum, as shown in Table 1, and the chemical structure was unambiguously established by the interpretation of the HMBC spectra obtained in CD_3OD and acetone-d_6. The hispidin moiety was assigned by the long-range correlations from H-4 to C-2 and C-5, H-6 to C-5 and C-8, H-7 to C-9 and C-13, H-9 to C-11 and C-13, H-12 to C-8 and C-10, and H-13 to C-7, C-9, and C-11, and these chemical shift values were in good agreement with the corresponding protons and carbons of known hispidin compounds.[14,15] The long-range correlations from H-2′ to C-4′, C-6′, and C-7′, H-5′ to C-1′ and C-3′, H-6′ to C-2′, C-4′, and C-7′, H-7′ to C-2′, C-6′, and C-9′, H-10′ to C-9′ and C-11′, and H-12′ to C-10′ and C-11′ revealed the presence of 6-(3,4-dihydroxyphenyl)-4-hydroxy-3,5-hexadien-2-one (hispolon). This partial structure reveals that the disappearance of the proton and carbon peaks of 10′ in the NMR spectra measured in CD_3OD was caused by deuterium exchange due to keto-enol tautomerism. An additional HMBC correlation from H-7′ to C-2 established the structure of **1**, as shown in Figure 2.

Compound **2** was obtained as a yellow amorphous powder, and its molecular formula, $C_{23}H_{18}O_8$, was established by the HRESIMS ion peak at *m/z* 423.1076 $[M+H]^+$ (calcd for $C_{23}H_{19}O_8$, 423.1074). This molecular formula requires 15 degrees of unsaturation. The IR spectrum exhibited bands due to hydroxyl (3420 cm^{-1}), conjugated carbonyl (1651 cm^{-1}), and aromatic (1603 and 1556 cm^{-1}) moieties. The UV maximum absorbance at λ_{max} (MeOH)(log ε) 221 (4.02), 255 (sh, 3.84), and 367 (3.85) nm suggested that **2** was also a hispidin analogue. The ^1H NMR spectrum of **2**, which was very similar to that of **1**, showed six aromatic methine signals assignable to two 1,2,4-trisubstituted benzenes, two singlets of sp^2 methine protons at δ 7.69 and 6.16, two olefinic doublets with *trans* geometry at δ 7.34 and 6.63, and a methyl singlet at δ 2.37. The structure of **2** was determined by the interpretation of the HMBC spectrum and comparison of the ^1H NMR spectra of **1** and **2**. The HMBC correlations for the hispidin moiety were consistent with those of **1**. Namely, long-range correlations were observed from H-4 to C-2 and C-5, H-6 to C-5 and C-8, H-7 to C-9 and C-13, H-9 to C-11 and C-13, H-12 to C-8 and C-10, and H-13 to C-7, C-9, and C-11. In addition, the HMBC correlations from H-7′ to C-2′, C-6′, and C-9′, and H-10′ to C-8′ and C-9′ revealed the presence of a 3,4-dihydroxybenzalacetone moiety. The above partial structures, viz.

Table 1. NMR data for interfungins A (**1**), B (**2**), and C (**3**) in CD_3OD[a]

No.	1		2		3	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1	165.9		166.1		166.2	
2	100.3		100.2		100.6	
3	170.0		170.3		170.7	
4	101.5	6.20 (1H, s)[b]	102.6	6.16 (1H, s)	102.5	6.16 (1H, s)
5	161.4		161.1		160.7	
6	116.8	6.65 (1H, d, J = 16.0)	117.1	6.63 (1H, d, J = 16.0)	117.0	6.63 (1H, d, J = 16.0)
7	137.6	7.37 (1H, d, J = 16.0)	137.2	7.34 (1H, d, J = 16.0)	137.0	7.34 (1H, d, J = 16.0)
8	128.9		128.3		129.0	
9	114.9	7.06 (1H, d, J = 2.0)	114.9	7.05 (1H, d, J = 2.0)	114.8	7.05 (1H, d, J = 2.0)
10	146.8		146.8		146.8	
11	148.7		148.6		148.6	
12	116.6	6.79 (1H, d, J = 8.0)	116.6	6.78 (1H, d, J = 8.0)	116.6	6.78 (1H, d, J = 8.0)
13	122.1	6.98 (1H, dd, J = 8.0, 2.0)	122.0	6.96 (1H, dd, J = 8.0, 2.0)	121.9	6.97 (1H, dd, J = 8.0, 2.0)
1′	128.8		127.9		128.4	
2′	117.3	6.94 (1H, d, J = 2.0)	117.6	6.98 (1H, d, J = 2.0)	117.2	6.96 (1H, d, J = 2.0)
3′	146.3		146.4		146.3	
4′	148.7		149.4		148.7	
5′	116.2	6.70 (1H, d, J = 8.4)	116.2	6.71 (1H, d, J = 8.4)	116.2	6.70 (1H, d, J = 8.0)
6′	124.9	6.84 (1H, dd, J = 8.4, 2.0)	125.6	6.88 (1H, dd, J = 8.4, 2.0)	124.8	6.84 (1H, dd, J = 8.0, 2.0)
7′	142.1	7.73 (1H, s)	145.8	7.69 (1H, s)	145.4	7.77 (1H, s)
8′	124.3		129.0		120.1	
9′	183.5		201.5		170.1	
10′	98.0[c]	Quenched	22.0	2.37 (3H, s)		
11′	195.7				52.6	3.75 (3H, s)
12′	26.0	2.06 (3H, s)				

[a] NMR data were recorded at 400 MHz for proton and at 100 MHz for carbon.
[b] Proton resonance integral, multiplicity, and coupling constant (J = Hz) are in parentheses.
[c] ^{13}C peak was quenched and assignment was carried out by HMBC correlation.

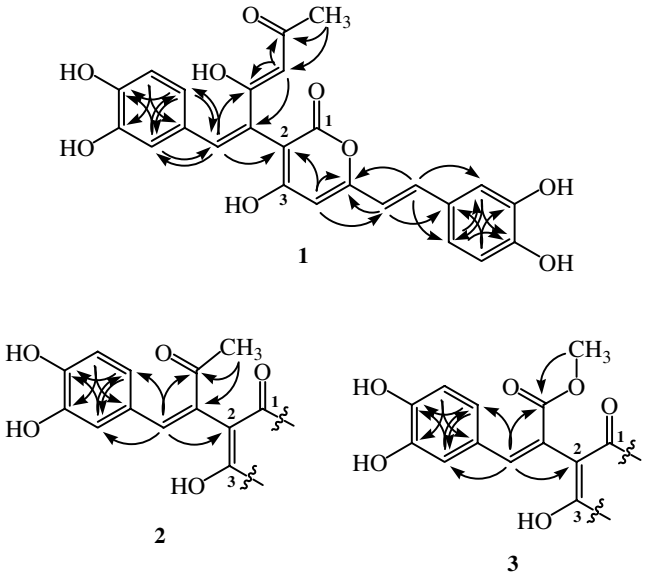


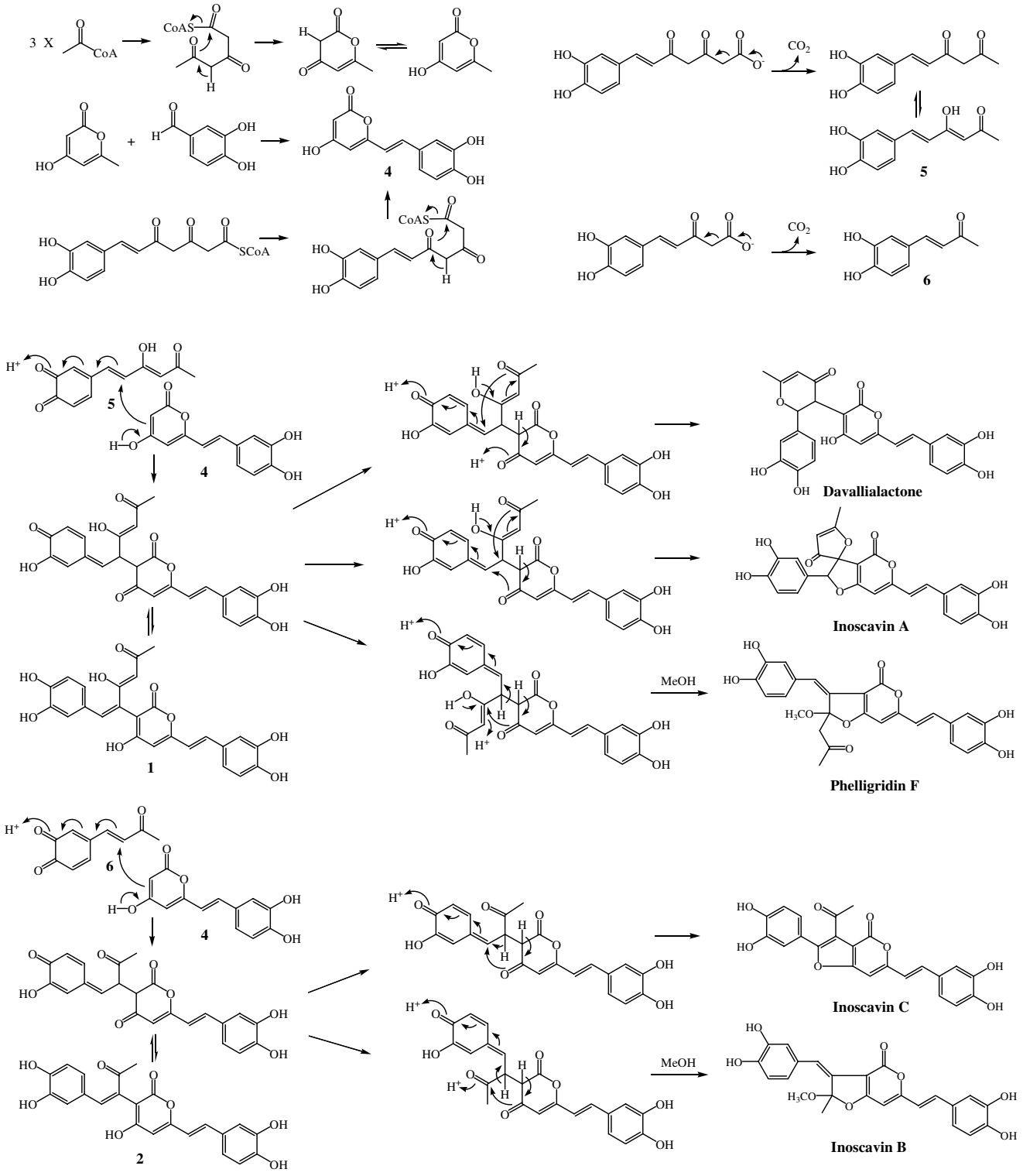
Figure 2. HMBC correlations of compounds **1**–**3**.

hispidin and dihydroxybenzalacetone, were unambiguously connected to each other by the three-bonded long-range correlation from H-7′ to C-2 (Fig. 2). Therefore, the structure of **2** was assigned as shown.

The molecular formula $C_{23}H_{18}O_9$ of **3** was determined by the HRESIMS measurement and suggested 15 degrees of unsaturation. Its IR and UV spectra similar to those of **2** indicated that the structure of **3** closely resembled to that of **2**. The ^1H and ^{13}C NMR spectra of **3** were also very similar to those of **2**, except for the presence of a methoxyl methyl group (δ_H 3.75, δ_C 52.6) instead of the acetyl methyl (δ_H 2.37, δ_C 22.0) in **2**. The structure of **3** was determined by the interpretation of two-dimensional NMR spectra including HMQC and HMBC. All proton-bearing carbons were assigned by the HMQC spectrum (Table 1), and the hispidin moiety was unambiguously established by the HMBC correlations and chemical shifts of corresponding carbons. Additional HMBC correlations from H-7′ to C-2′, C-6′, and C-9′, and H-11′ to C-9′ revealed the presence of a methyl caffeate moiety. The above partial structures, viz. hispidin and methyl caffeate, were connected to each other by the long-range correlation from H-7′ to C-2 (Fig. 2). We could not establish the geometry between C-7′ and C-8′ of **1**–**3** in spite of extensive NOE experiments. However, the rearrangement of **2** to inoscavin B at room temperature proposed their stereochemistry to be *cis*.

3. Biogenesis of antioxidant hispidins

The genera *Phellinus* and *Inonotus* produce a wide variety of polyphenolic compounds, such as inoscavins A–C, davallialactone, phelligridins A–G, and phelligridimer A, which possess the unique basic structural units, 6-[2-(3,4-dihydroxyphenyl)ethenyl]-4-hydroxy-2*H*-pyran-2-one (hispidin) and pyrano[4,3-c][2]benzopyran-1,6-



Scheme 1. Proposed biogenesis of hispidin class of antioxidants.

dione. Compounds **1**–**3**, which were isolated from the fruiting body of the fungus *I. xeranticus*, are highly oxygenated and functionalized aromatic compounds containing a hispidin moiety. Based on their chemical structures and the rearrangement of **2** to inoscavin B in MeOH at room temperature, we proposed a biogenetic mechanism for the formation of the mushroom polyphenolic compounds from the coupling of the precursor hispidin with 6-(3,4-dihydroxyphenyl)-4-hydroxy-3,5-hexadien-2-one (hispolon) or 4-(3,4-dihydroxyphenyl)-3-buten-2-one. Hispidin in mushrooms is known to be biosynthesized by two different mechanisms; one is from phenylalanine via a cinnamyl derivative that is combined with either acetate or malonate through the polyketide pathway,[14,16] and the other is by the condensation of 4-hydroxy-6-methyl-2-pyrone,

which is formed by the reaction of three molecules of acetyl-SCoA and one molecule of 3,4-dihydroxybenzoyl-SCoA (or 3,4-dihydroxybenzaldehyde).[9] From the above pathways, 6-(3,4-dihydroxyphenyl)-4-hydroxy-3,5-hexadien-2-one and 4-(3,4-dihydroxyphenyl)-3-buten-2-one might be biosynthesized by the coupling of 3,4-dihydroxybenzaldehyde and three or two acetate units, and the cinnamyl derivative and two or one acetate units, followed by a decarboxylation. Compounds **1** and **2** might be biogenerated by the condensation of **4** and **5**, and **4** and **6**, respectively, which is a process that could be catalyzed by mushroom peroxidase. The natural and/or enzymatic rearrangements of the highly functionalized compounds **1** and **2** may provide the mechanism for the formation of mushroom polyphenols such as inoscavins A–C, davallialactone, and phelligridin F, as depicted in Scheme 1.

4. Antioxidant activity

The antioxidant activity of **1**–**3** was evaluated by measuring their scavenging effects against the superoxide radical anion,[17] ABTS radical cation,[18] and DPPH radicals.[19] These compounds displayed significant antioxidant activity which was comparable to those of the well-known antioxidants, vitamin E and caffeic acid, which were used as controls (Table 2). **2** of the compounds tested exhibited most potent radical scavenging activity against all radical species tested.

5. Experimental

5.1. General methods

ESIMS was taken on a Navigator mass spectrometer in positive and negative modes, and HRESIMS was obtained on an ABI Mariner mass spectrometer with polyethylene glycol as internal standard. UV and IR spectra were recorded on a Shimadzu UV-300 and a FT-IR Equinox 55 spectrometer, respectively. NMR spectra were obtained on a Varian UNITY Inova NMR spectrometer with ^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz in CD_3OD or acetone-d_6. Chemical shifts are given in ppm (δ) using TMS as internal standard.

Table 2. Antioxidant activities of interfungins A (**1**), B (**2**), and C (**3**)[a]

Compounds	Superoxide radical[b]	ABTS radical[c]	DPPH radical[d]
1	6.3 ± 0.10	2.7 ± 0.81	14.1 ± 1.27
2	2.5 ± 0.21	1.8 ± 1.07	11.1 ± 1.84
3	3.7 ± 0.07	3.1 ± 0.64	11.1 ± 2.19
Vitamin E	>100	3.4 ± 0.64	11.6 ± 0.21
Caffeic acid	3.7 ± 0.14	2.2 ± 0.74	25.9 ± 2.27

[a] Presented as a mean (IC_{50}, μM) of triplicated experiments.
[b] Xanthin/xanthin oxidase.
[c] 2,2′-Azinobis(3-ethylbenzothiazoline-6-sulfonate).
[d] 1,1-Diphenyl-2-picrylhydrzyl.

5.2. Fungal materials

The specimen of the fungus *I. xeranticus* was collected in Chonan-si, Korea, in April 2005, and identified by staff at the Korea Research Institute of Bioscience and Biotechnology (KRIBB). A voucher specimen (No. Y011) was deposited in the herbarium of Antioxidants Research Laboratory, KRIBB.

5.3. Extraction and isolation

The ground fruiting bodies of *I. xeranticus* (3 kg) were extracted twice with methanol at room temperature for 2 days. After the removal of the methanol under reduced pressure, the resulting solution was partitioned first between *n*-hexane and H_2O, and then between ethyl acetate and H_2O. The ethyl acetate-soluble fraction was subjected to a column of Sephadex LH-20 eluted with $CHCl_3$:MeOH (1:1, v/v). The yellow antioxidant fraction exhibiting ABTS radical scavenging activity was concentrated and then chromatographed on a column of ODS by eluting with a gradient of increasing methanol content (40–100%) in water to afford two active yellow fractions. A yellow fraction was purified on a column of Sephadex LH-20 with 70% aqueous MeOH, followed by preparative reversed-phase TLC with 50% aqueous MeOH to provide **1** (5 mg, R_f 0.32) and **2** (7 mg, R_f 0.45). The other fraction was rechromatographed on a column of Sephadex LH-20 eluting with 70% aqueous MeOH, followed by reversed-phase TLC eluting with 50% MeOH to give **3** (4 mg, R_f 0.5).

5.3.1. Interfungin A (1). Yellow powder; UV (MeOH) λ_{max} (ε) 215 (4.24), 254 (4.04), 377 (4.25) nm; IR ν_{max} 3421, 1654, 1550, 1286, 1115 cm^{-1}; ^{1}H and ^{13}C NMR data in Table 1; (+)-LRESIMS *m*/*z* 487 $[M+Na]^+$; (−)-LRESIMS *m*/*z* 463 $[M-H]^-$; (+)-HRESIMS *m*/*z* 465.1200 $[M+H]^+$ (calcd for $C_{25}H_{21}O_9$, 465.1180).

5.3.2. Interfungin B (2). Yellow powder; UV (MeOH) λ_{max} (ε) 221 (4.02), 255 (sh, 3.84), 367 (3.85) nm; IR ν_{max} 3420, 1651, 1603, 1556, 1286, 1118 cm^{-1}; ^{1}H and ^{13}C NMR data in Table 1; (+)-HRESIMS *m*/*z* 423.1076 $[M+H]^+$ (calcd for $C_{23}H_{19}O_8$, 423.1074).

5.3.3. Interfungin C (3). Yellow powder; UV (MeOH) λ_{max} (ε) 221 (4.15), 254 (sh, 3.98), 373 (4.05) nm; IR ν_{max} 3437, 1651, 1599, 1556, 1441, 1250, 1116 cm^{-1}; ^{1}H and ^{13}C NMR data in Table 1; (+)-HRESIMS *m*/*z* 439.0990 $[M+H]^+$ (calcd for $C_{23}H_{19}O_9$, 439.1023).

5.4. Antioxidant activity

Antioxidant activity was evaluated by measuring free radical scavenging effects against the superoxide radical anion, ABTS radical cation, and DPPH radicals.

5.4.1. Superoxide radical anion scavenging activity. Superoxide anion scavenging activity was evaluated by the xanthine/xanthine oxidase method with minor modifications.[17] In brief, each well of a 96-well plate containing the 100 μL of the following reagents: 50 mM potassium phosphate buffer (pH 7.8), 1 mM EDTA,

0.04 mM NBT (nitroblue tetrazolium), 0.18 mM xanthine, 250 mU/mL xanthine oxidase, and samples. Plates were incubated for 30 min at 37 °C in the dark. The xanthine oxidase catalyzes the oxidation of xanthine to uric acid and superoxide, and the superoxide reduces NBT to blue formazan. The reduction of NBT to blue formazan was measured at 560 nm in a microplate reader. For each point, background was corrected by subtracting the values derived from the no-xanthine oxidase control.

5.4.2. ABTS radical cation decolorization assay. Evaluation of free radical scavenging activity was carried out by using ABTS radical cation decolorization assay.[18] The activity is based on the ability of the antioxidant to scavenge the radical cation 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonate) ($ABTS^{\cdot+}$) with spectrophotometric analysis. According to Re et al.,[18] ABTS was dissolved in H_2O to a concentration of 7 mM. The $ABTS^{\cdot+}$ cation radical was produced by reacting ABTS stock solution with 2.45 mM potassium persulfate (final concentration) and allowing the mixture to stand in the dark at room temperature for 12 h. After the addition of 0.1 mL of the ABTS radical cation solution ($A_{734\ nm} = 0.700$) to the ethanol solution of the compound (5 μL) and mixing for 6 min, the absorbance was measured by ELISA reader using VERSAmax (Molecular Devices Co., USA).

5.4.3. DPPH radical scavenging activity. Sample dissolved in 5 μL of DMSO was added to 95 μL of 150 μM DPPH ethanol solution. After vortex mixing, the mixture was incubated for 20 min at room temperature, and the absorbance was measured at 517 nm using an ELISA reader (Molecular Devices Co., USA).[19] The differences in absorbance between the test sample and control (DMSO) were measured. Vitamin E and caffeic acid were used as standards.

Acknowledgments

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