Sesquiterpenes and polyphenols with glucose-uptake stimulatory and antioxidant activities from the medicinal mushroom

_Sanghuangporus sanghuang_

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**[ABSTRACT]** A chemical investigation on the fermentation products of _Sanghuangporus sanghuang_ led to the isolation and identification of fourteen secondary metabolites (1–14) including eight sesquiterpenoids (1–8) and six polyphenols (9–14). Compounds 1–3 were sesquiterpenes with new structures which were elucidated based on NMR spectroscopy, high resolution mass spectrometry (HRMS) and electronic circular dichroism (ECD) data. All the isolates were tested for their stimulation effects on glucose uptake in insulin-resistant HepG2 cells, and cellular antioxidant activity. Compounds 9–12 were subjected to molecular docking experiment to primarily evaluate their anti-coronavirus (SARS-CoV-2) activity. As a result, compounds 9–12 were found to increase the glucose uptake of insulin-resistant HepG2 cells by 18.1%, 62.7%, 33.7% and 21.4% at the dose of 50 μmol·L⁻¹, respectively. Compounds 9–12 also showed good cellular antioxidant activities with CAAS values of 12.23, 23.11, 5.31 and 16.04 μmol·L⁻¹, respectively. Molecular docking between COVID-19 Mpro and compounds 9–12 indicated potential SARS-CoV-2 inhibitory activity of these four compounds. This work provides new insights for the potential role of the medicinal mushroom _S. sanghuang_ as drugs and functional foods.

**[KEY WORDS]** _Sanghuangporus sanghuang_; Sesquiterpenoids; Polyphenols; Glucose-uptake stimulation; Cellular antioxidant activity; Anti-coronavirus activity

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**Introduction**

Edible and medicinal mushrooms such as _Ganoderma* lingzhi* and *Wolffiporia coco*l are valuable materials for the production of healthy foods and medicines for various diseases [1–4]. Recently, the traditional medicinal mushroom “Sanghuang” has been identified as _Sanghuangporus sanghuang_ by Dr. WU Sheng-Hua and other colleagues [9,10]. Due to their diverse and potent bioactivities such as anti-oxidation, anti-tumor, immunomodulation, liver protection and anti-inflammatory [11–13], _S. sanghuang_ and its phylogenetically related species are widely used as folk medicines in China, Japan, and Korea.

In recent decades, the prevalence of diabetes characterized with insulin resistance and raised blood sugar has been demonstrated all over the world. Medicines and health food conducive to prevent and treat diabetes are in great needs. The polysaccharides or extracts of _S. sanghuang_ and some phylogenetically related species show potentials in decreasing hyperglycemia [14,18]. However, secondary metabolites responsible for the observed hypoglycemic activity from _Sanghuangporus_ mushrooms were seldom investigated. Moreover, small quantities in natural surroundings and difficulties in cultivation of the fruit bodies of _S. sanghuang_ limited its wide application and development.

Recently, the fermentation product of _S. sanghuang_ that is easier to obtain in industry attracts increasing attention due to its similar bioactivities to the fruiting bodies [16]. In the current work, a systematic phytochemical investigation on the fermented mycelia and broth extract of _S. sanghuang_ was carried out. As a result, fourteen compounds (1–14) were ob-
Results and Discussion

The ethyl acetate soluble fraction obtained from the ethanol extract of *S. sanghuang* was separated by a combination of chromatographic methods including ODS, Sephadex LH-20 and preparative HPLC to yield three new sesquiterpenes (1–3), five known sesquiterpenes including (−)-(1’S, 3’S)-(2′E, 4′E)-3′-hydroxy-γ-ionylidenacetoc acid (4) [17], phellisin G (5) [18], phellisin L (6) [18], elegone D (7) [19], 2′-[4′-(4-Methyl-3-cyclohexene-1α-yl)-5-deoxy-alpha-d-lyxofuranosyl]propanoic acid (8), four known polyphenols including hispidin (9) [20], 3′, 14′-bihispidinyl (10) [21], davallialactone (11) [22], and baumin (12) [23], and two polyphenols with ketenol tautomism including hispolone (13) [24], and interfungin A (14) [25] (Fig. 1). The structures of the known compounds were determined by comparing their NMR and MS data with previous data. The structures of new compounds are elucidated as follows:

Compound 1 was isolated as colorless powder with the molecular formula C₁₅H₂₃O₄ (5 degrees of unsaturation) deduced by HR-ESIMS data ([M + H]+, m/z 267.1599; Calcd. 267.1596). Its 1H, 13C NMR (Table 1) and HSQC spectra showed the presence of fifteen carbon signals which were further identified as three methyls [δ_H/δ_C 0.98 (s)/30.2, 1.07 (s)/29.1, 2.05 (d, J = 1.3 Hz)/15.1], three methylenes including one oxygenated [δ_H/δ_C 0.95 (d, J = 11.2 Hz), 1.23 (d, J = 11.2 Hz)/43.6, 1.45 (dd, J = 13.7, 9.6 Hz), 2.10 (dd, J = 13.7, 7.1 Hz)/31.7; 3.58 (d, J = 8.1 Hz), 3.74 (d, J = 8.1 Hz)/73.9], five methines including two oxygenated and one sp² methine [δ_H/δ_C 0.51 (d, J = 4.1 Hz)/33.3, 1.26 (d, J = 4.1 Hz)/29.4, 3.64 (m)/63.0, 4.14 (s)/85.2, 5.71 (t, J = 1.3 Hz)/114.5], three quaternary carbons (δ_C 29.6, 30.5, 157.6) and a carboxyl carbon (δ_C 167.5) in structure (Table 1). The HMBC correlations from H-10 to C-9, C-11; from H₂-12 to C-9, C-10; from H-8 to C-7, C-9; from H₂-2 to C-3; from H-3 to C-1, C-4, C-5; from H-6 to C-1, C-5; from H-7 to C-5; from H-8 to C-7, C-13; from H₂-13 to C-5; from H₋14 to C-1, C-2; from H₋15 to C-1, C-6; as well as the 1H-1H COSY correlations of H-6/H-7/H-8 and H₂-2/H-3/H-4 (Fig. 2) indicated the sesquiterpenoid skeleton for 1. In addition, the HMBC correlations from H₋4 and H₋13 to C-7, and from H-8 to C-13 together with the unsaturation degrees of 1 confirmed the linkage of C₅–C₇ and the presence of one ether bond between C-8 and C-13 as shown in Fig. 2. The planar structure of 1 was finally determined to be a 6−3−5 membered fused ring system similar to the structure of phellin C [26], except for a hydroxyl group substituted at C-3 in 1.

The relative configuration of 1 was determined by analysis of NOE correlations and the coupling constants. The NOE correlations of H₋15 with H-3 and H-7, H-6 with H-8 and H₋14 as well as the coupling constant near to zero between H-7 and H-8 (the dihydral angel of near to 90 degree) indicated α configuration for H-3, H-7 and H₋15, β configuration for H-6, H-8 and H₋14 (Fig. 3). The geometrical configuration of the double bond at C-9 was confirmed as E, on the basis of the key NOE correlations (H-10 with H-8 and H₋13). The Rh₂(CO)₂Cl₂-induced ECD method was conducted to clarify the absolute configuration of compound 1 [27]. According to Snatzke’s bulkiness rule, the induced positive Cotton effects at approximately 350 nm (E band) in
Fig. S2A elucidated the 3S configuration in 1. Combining the relative configuration established above, the absolute configuration of compound 1 was determined as 3S, 5S, 6S, 7R and 8R, which was further proved by the calculated ECD results (Fig. S2B).

Compound 2 was isolated as yellow powder with the molecular formula of C_{13}H_{22}O_{4} and five degrees of unsaturation deduced from HR-ESIMS data. The 1D and 2D NMR data (Table 1) for 2 indicated a similar structure to that of 7, with the methylene group at C-12 replaced by an oxygenated methine resonating at δ 72.3. The HMBC correlations (Fig. 3) of H-7 to C-8, C-12, H-12 to C-8, C-10 and the 'H-'H COSY correlations between the oxymethine proton (δ 4.20) and H-7, H-11 further confirmed the location of one hydroxyl group at C-12. The chemical shift value of C-5 (δ 80.1) in 2 moved to the low field significantly compared with that of 7, which in combination with the requirement of unsaturation degrees supports the presence of an ester bond between C-1 and C-5, giving a six-membered lactone ring. The free rotation around C-6 was hindered, due to the formation of lactone ring in 2. After conformation searching optimization using xtb and Gaussian program, the minimum energy conformation with above 90% Boltzmann distribution was obtained. The NOE correlations of H_{14}-14 with H-12, H_{2}-4 and H-7, H-5 with H_{2}-8δ (δ_{6} 1.24) and proton at 6-0H with H_{2}-8α (δ_{6} 1.71) analyzed at the optimal conformation assigned the relative configuration of 2. To determine the absolute configurations, the ECD spectra of stereoisomers 2a (5R/6R/7R/12S) and 2b (5S/6S/7S/12R) was calculated. As shown in Fig. S2C, the calculated ECD curve of 2a was in good agreement with the experimental CD spectrum of 2. Thus, the absolute configuration of 2 was established as 5R, 6R, 7R and 12S.

Compound 3 was obtained as colorless powder and its positive HR-ESIMS showed a molecular ion peak at m/z 267.1792 corresponding to a molecular formula of C_{15}H_{22}O_{4}. The 1D and 2D NMR data (Table 1) of 3 were similar to those of 2, with the only differences in the chemical shifts of C-5 (δ 72.6) and C-6 (δ 86.0). The HMBC correlations of the active hydrogen δ 4.87 (d, J = 6.5 Hz) with C-4, C-5 and C-6 further confirmed the presence of a hydroxyl group at C-5. The change in the chemical shift of C-5 and C-6 as well as the requirement of unsaturation degrees indicated an ester bond between C-1 and C-6 forming a seven-membered lactone ring. Because of the formation of a seven-membered lactone, the steric hindrance limited the rotation around C6-C7. The key NOE correlations of H_{14}-14 with 5-OH/H-7/H-12 at the minimum energy conformation obtained from the conformation searching using xtb and Gaussian program, as well as the small coupling constant of 4.0 Hz between H-7 and H-12 confirmed the same orientation for for H-7, H-12, H_{14}-14 and 5-OH. The calculated ECD curve of stereoisomers 3a (5S/6R/7R/12S) matched with the experimental CD spectrum of 3 (Fig. S2D). Thus, the absolute configuration of 3 was confirmed as 5S, 6R, 7R and 12S.

Signals in the NMR spectra of compounds 13–14 occurred in pairs. Compounds 13–14 were finally identified as two pairs of keto-enol tautomers by comparison with previous data. The major set of NMR signals were attributed to the enol form of hispolone, and interfungin A, while the minor set of NMR signals was determined to be the corresponding keto structures. The interconversion referring to the chemical equilibrium between the ketone and enol structures is a very common phenomenon in natural products with conjugated dien-2-ol structural feature \cite{24, 25, 28-30}.

**Evaluation of Biological Activities**

All the isolates were tested for their stimulatory effects on glucose uptake in insulin-resistant HepG2 cells, cellular antioxidant activity and potential inhibitory effects on 2019-nCoV protease.

**Glucose uptake-stimulation activity**

As mentioned above, the crude extract of phylogenetically related species of S. sanghuang exhibited good hypoglycemic activity. Accordingly, all the isolates from S. sanghuang were evaluated for their effects on glucose uptake in insulin-resistant HepG2 cells. All the compounds showed no obvious cytotoxicity against HepG2 cells at the dose of 100 μmol·L^{-1}. As shown in Fig. 4, sesquiterpenes 1 and 8 and polyphenols 9–12 effectively enhanced the insulin-stimulated uptake of 2-NBDG in insulin-resistant HepG2 cells by 36.6%, 50.7%, 48.2%, 59.5%, 45.5% and 46.0% at the dose of 100 μmol·L^{-1}, respectively. Polyphenolic compounds 9–12 showed relatively stronger hypoglycemic activity than sesquiterpenes obtained in this work. At the dose of 50 μmol·L^{-1}, 9–12 showed the most promising activity with the increase of glucose uptake by 18.1%, 62.7%, 33.7% and 21.4% respectively.

**Cellular antioxidant activity**

All the isolates were evaluated for their antioxidant activity using HepG2 cells-based method that is more accurate and biologically relevant than the commonly used DPPH and ABTS free radical scavenging experiments \cite{31, 32}. As shown in Fig. S4 and Table 2, polyphenols (9–12) showed good cellular antioxidant activity in a dose-dependent manner and their CAA50 (cellular antioxidant activity value) values were in a range of 5.31–23.11 μmol·L^{-1}. Sesquiterpenes 1–8 exhibited weak antioxidant activity with CAA50 values larger than 100 μmol·L^{-1}.

**Molecular docking analysis of polyphenols and COVID-19 M^pro**

A previous work presented the potential of hispidin...
against 2019-nCoV protease by molecular docking study \(^{[35]}\), which indicated that hispidin or those containing hispidin fragment might be a potential bioactive compound against COVID-19. Therefore, molecular docking analysis of the isolated polyphenols (9–12) and COVID-19 M\(^{\text{pro}}\) was conducted to preliminarily predict the COVID-19 inhibitory activity. As shown in Fig. S6, compounds 9–12 and remdesivir bound tightly in the active pocket of the enzyme with low binding energy (9: −7.10 kcal mol\(^{-1}\); 10: −9.10 kcal mol\(^{-1}\); 11: −8.40 kcal mol\(^{-1}\); 12: −8.10 kcal mol\(^{-1}\); remdesivir: −7.70 kcal mol\(^{-1}\)). The H-bond interactions between the hydroxyl and carbonyl residues of the inhibitors and the indicated amino acid residues T24, S46, F140, L141, G143, S144, C145, H163 and Q189 in the active site of COVID-19 M\(^{\text{pro}}\) are shown in Figs. S6B–F. These results were consistent with the earlier findings that the inhibitors interacted with the amino acid residues surrounding the important residues H41, C145 and G166 in the substrate-binding subsite S1 and the neighboring area \(^{[34]}\).

Insulin resistance and oxidative stress damage are two important pathological factors involved in the development of diabetes \(^{[36–38]}\). Polyphenolic compounds 9–12 isolated from \(S.\) sanghuang exhibited not only good hypoglycemic activity but also excellent antioxidant activity, supporting the potential of this mushroom in the treatment of diabetes and its related complications.

**Experimental**

**General experimental procedures**

Octadeclisililic silica gel (ODS, 50 μm, YMC Co., Ltd., Kyoto, Japan) and Sephadex LH-20 (GE Healthcare Bio-Science AB, Uppsala, Sweden) were used for column chromatography. High-performance liquid chromatography (HPLC) separation was conducted on an Agilent 1200 HPLC system (Agilent Technologies, Inc., USA) with a reversed-phase column (C\(_{18}\), 250 mm × 9.4 mm, 5 μm, YMC Pack, YMC Co., Ltd., Japan) at a flow rate of 2.0 mL min\(^{-1}\). Solvent used for extraction and separation was of analytical grade and chromatographical grade solvent was used for HPLC. TLC was carried out on silica gel HSGF\(_{254}\) (Qingdao Marine Chemical Co. Ltd., Qingdao, China) and spots were visualized by UV at 254 nm and being heated after spraying with 10% H\(_2\)SO\(_4\). NMR spectral data were obtained with a Bruker AVANCE-500 spectrometer (Karlsruhe, Germany) in DMSO-d\(_6\) (δ\(_C\) 2.50, 3.33; δ\(_H\) 39.5). High-resolution electrospray ionization mass spectrometry (HR-ESIMS) data were obtained by an Agilent Accurate-Mass-Q-TOF LC/MS 6520 instrument (Agilent Technologies, Inc., USA). The IR spectra were measured by a JASCO J-815 Spectropolarimeter (JASCO, Easton, MD, USA). UV data was acquired by a Thermo Genesyss-10S UV-Vis (Thermo Fisher Scientific Inc., USA). Optical rotation values were measured on an Anton Paar MCP 200 automatic polarimeter (Anton Paar, Inc., Austria).

**Fungal material**

\(Sanghuangporus\) sanghuang was identified by Professor Wu Sheng-Hua in Museum of Natural Science in Taiwan and fermented as previously reported \(^{[39]}\).

**Extraction and isolation**

The mycelia and broth of \(S.\) sanghuang was lyophilized and further extracted by ethanol (1L × 3) with ultrasonication. The organic solvent was filtered and evaporated to dryness under vacuum to afford a crude extract (27.0 g). The ethanol extract was suspended in water (1000 mL) and partitioned with hexane and ethyl acetate (EtOAc), respectively. The EtOAc fraction (10.2 g) was then subjected to ODS column chromatography (CC) using a gradient methanol-water (10%–90%) to give 16 subfractions (SH-1–SH-16).

Fraction SH-8 eluted with 50% methanol–water was further separated by Sephadex LH-20 CC using 80% methanol–water to afford 16 subfractions (SH-8-1–SH-8-16). SH-8-4 (19.0 mg) was further separated by RP-HPLC using 30% acetonitrile in water to give compound 13 (10.0 mg, \(t_R\) 21.8 min). SH-8-7 (500.0 mg) was further separated by RP-HPLC using 33% acetonitrile in water to give compound 9 (390.0 mg, \(t_R\) 19.7 min). SH-8-9 (88.0 mg) was further separated by RP-HPLC using 30% acetonitrile in water to give compound 14 (72.0 mg, \(t_R\) 20.3 min), SH-8-11 (330.0 mg) was further separated by RP-HPLC using 32% acetonitrile in water to give compound 10 (190.0 mg, \(t_R\) 17.3 min).

Fraction SH-10 eluted with 60% methanol–water was further separated by Sephadex LH-20 CC using 80% methanol–water to afford 13 subfractions (SH-10-1–SH-10-13). SH-10-2 (23.0 mg) was further separated by RP-HPLC using 40% acetonitrile in water to give compounds 1 (1.5 mg, \(t_R\) 24.5 min), 2 (2.0 mg, \(t_R\) 25.1 min) and 3 (1.5 mg, \(t_R\) 26.5 min). SH-10-6 (1.0 g) was further separated by ODS CC using a gradient methanol–water (20%–80%) to give 10 subfractions (SH-10-6-1–SH-10-6-10). SH-10-6-6 (29.0 mg) was further purified by RP-HPLC using 33% acetonitrile in water to give compound 7 (2.9 mg, \(t_R\) 27.9 min). SH-12-2 (11.8 mg) was further purified by RP-HPLC using 35% acetonitrile in water to give particle.
compounds 5 (1.3 mg, \( t_R \) 28.6 min) and 6 (0.6 mg, \( t_R \) 28.9 min). SH-12-4 (28.0 mg) was further separated by preparative TLC (PTLC) using dichloromethane/methanol (10 : 1, V/V) as the developing solvent to give 6 fractions (SH-12-4-1–SH-12-4-6). SH-12-4-1 (11.0 mg) was further purified by RP-HPLC using 32% acetonitrile in water to give compound 8 (4.0 mg, \( t_R \) 29.6 min). SH-12-4-4 (11.0 mg) was further separated by RP-HPLC using 33% acetonitrile in water to give compound 4 (2.0 mg, \( t_R \) 30.0 min). The presence of all the isolated compounds in the EtOH extract (10 mg mL\(^{-1}\)) were indicated by HPLC with a gradient elution (0–30 min: 5%–50% acetonitrile in water; 30–50 min: 50%–75% acetonitrile in water; 50–60 min: 100% acetonitrile; flow rate: 1 mL min\(^{-1}\)) at 210 and 300 nm (Fig. S1).

Compound 1: colorless powder; [\( \alpha \)]\(_D\) \( ^{25} \) \(-40.99 (c 0.1, MeOH); UV (MeOH) \( \lambda_{\text{max}} \) (log e) 209 (3.92), 230 (0.81) nm; CD (c 1.89 \( \times \) \( 10^{-3} \) mol L\(^{-1}\), MeOH) \( \lambda_{\text{max}} \) (\( \Delta \varepsilon \)) 208 (+0.39), 232 (–0.43) nm; \(^1\)H and \(^{13}\)C NMR data, Table 1; HR-ESIMS m/z [M + H\(^+\)]: 267.1599 (Calcd. for C\(_{15}\)H\(_{23}\)O\(_{4}\)).

Compound 2: yellow powder; [\( \alpha \)]\(_D\) \( ^{25} \) +36.60 (c 0.1, MeOH); UV (MeOH) \( \lambda_{\text{max}} \) (log e) 211 (3.83) nm; CD (c 1.94 \( \times \) \( 10^{-3} \) mol L\(^{-1}\), MeOH) \( \lambda_{\text{max}} \) (\( \Delta \varepsilon \)) 209 (+10.9), 229 (–0.6) nm; \(^1\)H and \(^{13}\)C NMR data, Table 1; HR-ESIMS m/z [M + H\(^+\)]: 267.1592 (Calcd. for C\(_{15}\)H\(_{23}\)O\(_{4}\)).

Compound 3: colorless powder; [\( \alpha \)]\(_D\) \( ^{25} \) +6.99 (c 0.1, MeOH); UV (MeOH) \( \lambda_{\text{max}} \) (log e) 210 (4.37) nm; CD (c 1.93 \( \times \) \( 10^{-3} \) mol L\(^{-1}\), MeOH) \( \lambda_{\text{max}} \) (\( \Delta \varepsilon \)) 209 (+9.0), 230 (–0.4) nm; \(^1\)H and \(^{13}\)C NMR data, Table 1; HR-ESIMS m/z [M + H\(^+\)]: 267.1792 (Calcd. for C\(_{15}\)H\(_{23}\)O\(_{4}\)).

**ECD calculations**

Systematic conformation analysis of 1a, 2a, 3a was conducted with xtb, using the GFN0-xTB at 298.15 K and GFN2-xtB at gbsa solvent model (methanol). Optimization with DFT calculation at the B3LYP-D3(BJ)/6-31G\(^*\) level in MeOH by the Gaussian16 program (Revision C.01, Gaussian Inc., USA) afforded the MMFF minima. The overall ECD spectra were then produced with an inhibitor N3 (PDB ID: 6LU7) was obtained from the RCSB Protein Data Bank (PDB) database. The overall inhibitor and water molecules were deleted from the crystal structure before docking simulation using PyMOL and the protein was saved in PDB format (receptor.pdb). The ligand structures were first drawn using ChemBioOffice software (version 14.0) and converted to 3D structures by ChemBio 3D software. Then the 3D structures were subjected to energy minimization using the MM2 menu in ChemBio 3D and deposed as files in PDB format (ligand.pdb). Both of the receptor.pdb and ligand.pdb were transformed to PDBQT format by AutoDockTools for the subsequent docking. Docking simulation was conducted using AutoDock Vina [42] and the docking calculation results were analyzed using PyMOL.

**Conclusions**

A total of eighteen secondary metabolites including three new sesquiterpenes (1–3) were identified from the culture of S. sanghuang. The glucose uptake stimulating activity, the antioxidant activity and the potential anti-SARS-CoV-2 activity detected for the secondary metabolites hispidin (9), 3, 14-

**Evaluation of cellular antioxidant activity**

HepG2 cells were routinely cultured in Dulbecco’s Modified Eagle medium (DMEM) and this experiment was carried out as previously reported with minor modification [40]. HepG2 cells were incubated in 96-well plate at a density of \( 1 \times 10^4 \) cells/well. After reaching confluence, serial dilutions of the compounds and positive drug (quercetin, aladin, Aladdin Biochemical Technology Co., Ltd., Shanghai, China) from 100 μmol L\(^{-1}\) were added and incubated for 24 h. Then 25 μmol L\(^{-1}\) 7’-dichlorodihydrofluorescein diacetate (DCFH-DA, aladin, Aladdin Biochemical Technology Co., Ltd., Shanghai, China) probe was added and incubated at 37 °C for 1 h. After that, the cells were washed with ice-cold PBS and then, 100 μL 600 μmol L\(^{-1}\) 2’-azobis (2-methylpropion-amidine) dihydrochloride (ABAP, aladin, Aladdin Biochemical Technology Co., Ltd., Shanghai, China) was added. The fluorescence intensity of the compounds and positive drug (quercetin, aladin, Aladin Biochemical Technology Co., Ltd., Shanghai, China) was added and incubated for 30 min. Finally, the cells were washed with PBS and 100 μL FBS-free DMEM was added to each well. The fluorescence intensity of 2-NBDG was measured by a microplate reader at 485 nm excitation and 528 nm emission. Five replicate wells were included, and each experiment was repeated three times. All the data were processed with GraphPad Prism 5 (GraphPad Software, USA) and presented as mean ± SD of three independent experiments.
bihispidinyl (10), davallialactone (11), and baumin (12) of S. sanghuang indicate the therapeutic effects of S. sanghuang on diabetes and coronavirus infection, and provide new insights of the bioactive secondary metabolites produced by S. sanghuang.

**Supporting Information**

Supporting information of this paper can be requested by sending E-mails to the corresponding authors.

**References**


**Table 1** ¹H (500 MHz) and ¹³C (125 MHz) NMR Data of 1–3 in DMSO-d₆

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<td>73.9</td>
<td>3.74 d (8.1)</td>
</tr>
<tr>
<td>14</td>
<td>30.2</td>
<td>0.98 s</td>
<td>23.3</td>
<td>21.2</td>
<td>30.2</td>
<td>0.98 s</td>
</tr>
<tr>
<td>15</td>
<td>29.1</td>
<td>1.07 s</td>
<td>12.4</td>
<td>17.0 s</td>
<td>29.1</td>
<td>1.07 s</td>
</tr>
<tr>
<td>16-COOH</td>
<td>5.48 d (8.1)</td>
<td>4.44 d (4.6)</td>
<td>12.4</td>
<td>17.0 s</td>
<td>5.48 d (8.1)</td>
<td>4.44 d (4.6)</td>
</tr>
<tr>
<td>3-OH</td>
<td>12.0</td>
<td>4.87 d (6.5)</td>
<td>12.4</td>
<td>17.0 s</td>
<td>12.0</td>
<td>4.87 d (6.5)</td>
</tr>
<tr>
<td>5-OH</td>
<td>12.0</td>
<td>4.87 d (6.5)</td>
<td>12.4</td>
<td>17.0 s</td>
<td>12.0</td>
<td>4.87 d (6.5)</td>
</tr>
<tr>
<td>6-OH</td>
<td>12.0</td>
<td>4.87 d (6.5)</td>
<td>12.4</td>
<td>17.0 s</td>
<td>12.0</td>
<td>4.87 d (6.5)</td>
</tr>
<tr>
<td>11-COOH</td>
<td>12.0</td>
<td>4.87 d (6.5)</td>
<td>12.4</td>
<td>17.0 s</td>
<td>12.0</td>
<td>4.87 d (6.5)</td>
</tr>
</tbody>
</table>

**Table 2** Cellular antioxidant activity of 9–12 (mean ± SD, n = 3)

<table>
<thead>
<tr>
<th>Compounds</th>
<th>CAA₅₀(μmol·L⁻¹)</th>
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<tbody>
<tr>
<td>9</td>
<td>12.2 ± 1.2</td>
</tr>
<tr>
<td>10</td>
<td>23.1 ± 1.2</td>
</tr>
<tr>
<td>11</td>
<td>5.3 ± 1.3</td>
</tr>
<tr>
<td>12</td>
<td>16.0 ± 1.1</td>
</tr>
<tr>
<td>Quercetin</td>
<td>&lt; 1</td>
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</tbody>
</table>


