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ORIGINAL ARTICLE

Five undescribed plant-derived bisphenols from *Artemisia capillaris* aerial parts: Structure elucidation, anti-hepatoma activities and plausible biogenetic pathway

Lanlan Ge [a,b], Qiujie Xie [a], Xiaofang Wei [a,c], Yangfang Li [a], Wanying Shen [a,c], Yunguang Hu [d], Jie Yao [a], Shuling Wang [e], Xiao Du [e,f,*], Xiaobin Zeng [a,b,g,*]

[a] *Center Lab of Longhua Branch and Department of Infectious Disease, Shenzhen People's Hospital (The Second Clinical Medical College, Jinan University; The First Affiliated Hospital, So uthern University of Science and Technology), Shenzhen 518020, Guangdong Province, PR China*
[b] *Department of pathology (Longhua Branch), Shenzhen People's Hospital (The Second Clinical Medical College, Jinan University; The First Affiliated Hospital, Southern University of Science and Technology), Shenzhen 518120, Guangdong Province, PR China*
[c] *College of pharmacy, Gansu University of Chinese Medicine, Lanzhou 730000, Gansu Province, PR China*
[d] *Guangdong Yifang Pharmaceutical Co., Ltd., Foshan 528241, Guangdong Province, PR China*
[e] *College of Pharmacy, School of Medicine, Hangzhou Normal University, Hangzhou 311121, Zhejiang Province, PR China*
[f] *China Resources Sanjiu Medical & Pharmaceutical Co., Ltd., Shenzhen 518110, Guangdong Province, PR China*
[g] *Guangdong Provincial Key Laboratory of Regional Immunity and Diseases, Medicine School of Shenzhen University, Shenzhen 518037, Guangdong Province, PR China*

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KEYWORDS

Artemisia capillaris;
Bisphenols;
Structure elucidation;

Abstract Yin-Chen, which belongs to the *Asteraceae* family and the genus *Artemisia*, is among the most abundantly used traditional medicines in China for the treatment of hepatitis and bilious disorder. Herein, five undescribed plant-derived bisphenols, capillarisenols A–E (**13**, **15**, **25**, **29**, **31**), and one undescribed phenolic compound (**32**), together with 32 known phenolic compounds

* Corresponding authors at: College of Pharmacy, School of Medicine, Hangzhou Normal University, Hangzhou 311121, Zhejiang Province, PR China (Xiao Du) and Center Lab of Longhua Branch and Department of Infectious Disease, Shenzhen People's Hospital (The Second Clinical Medical College, Jinan University; The First Affiliated Hospital, So uthern University of Science and Technology), Shenzhen 518020, Guangdong Province, PR China (Xiaobin Zeng).
E-mail addresses: duxiao9@999.com.cn (X. Du), zeng.xiaobin@szhospital.com (X. Zeng).

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Plausible biogenetic pathway;
Anti-hepatoma activity

(**1**–**12**, **14**, **16**–**24**, **26**–**28**, **30**, **33**–**38**), were isolated and identified based on spectroscopic evidence from aerial parts of *Artemisia capillaris* Thunb. Capillarisenols A–E are the type of bisphenols firstly isolated from this plant. The plausible biogenetic pathway of new compounds was also proposed. In addition, the potential anti-hepatoma effects on Huh7 and HepG2 cell lines of all isolated compounds were evaluated in vitro. Capillarisenol C (**25**) showed significant anti-hepatoma activity in Huh7 and HepG 2 cells, with IC_{50} values of 4.96 and 8.58 μM, better than the positive control drug (Lenvatinib). This study provided phytochemical evidence for further development and utilisation of *A. capillaris* in health products.

1. Introduction

Yin-Chen, which belongs to the Asteraceae family and the genus Artemisia, is among the most abundantly used traditional medicines in China for the treatment of hepatitis and bilious disorder (Jang, et al., 2015; Zhao, et al., 2014). Two species, *Artemisia scoparia* Waldst. et Kit and *Artemisia capillaris* Thunb., are documented in the Chinese Pharmacopoeia as authentic Yin-Chen resources (Chinese Pharmacopoeia Commission, 2015). In Guangdong, China, Yin Chen and fried crucian carp are boiled in soup, which can effectively soothe the liver and clear liver heat. This is a commonly used local soup food therapy. Modern pharmacological studies have shown that *A. scoparia* and *A. capillaris* have a broad spectrum of biological activities, including antiviral, antitumor, anti-bacterial, anti-inflammatory, antioxidant, anti-cirrhosis and hepatoprotective effects (Ding, et al., 2021; Hsueh, et al., 2021). Most of the therapeutic effects can be attributed to the major or minor compounds found in this medicinal herbs, for example, flavonoids and coumarins (Cai, et al., 2020; Geng, et al., 2015; Lee, et al., 2007; Wang, et al., 2008). In addition, phytochemical assessments have found that Yin-Chen also contains other compounds, such as flavonoid glycosides, volatile oil, steroids, chromones, coumarin, phenolic acids and terpenoids (Aati, et al., 2020; Ding, et al., 2021; Hsueh, et al., 2021; Tian, et al., 2020).

As part of the ongoing search for promising new anti-liver compounds from traditional medicinal plants, bioactivity-guided isolation and fraction of *A. capillaris* aerial parts were carried out. Five undescribed bisphenols, capillarisenols A–E (**13**, **15**, **25**, **29**, **31**), and one undescribed phenolic compound (**32**), together with 32 known phenolic compounds (**1**–**12**, **14**, **16**–**24**, **26**–**28**, **30**, **33**–**38**) were isolated and identified. The chemical structures of all identified compounds are shown in Fig. 1. Capillarisenols A–E (**13**, **15**, **25**, **29**, **31)** are the naturally occurring bisphenols firstly isolatedfrom this plant. Here, we describe the structural elucidation and plausible biogenetic pathway of new compounds. In addition, the potential anti-hepatoma effects of all isolated compounds on Huh7 and HepG 2 cells were evaluated.

2. Materials and methods

2.1. General experimental procedures

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DPX-400 (^{1}H NMR, 400 MHz; ^{13}C NMR, 100 MHz) spectrometer, with tetramethylsilane (TMS) as the internal standard. Unless otherwise specified, chemical shifts (δ) were quoted in ppm with reference to the residual solvent signal (DMSO d_6: δ_H 2.50 ppm, δ_C 39.52 ppm). Positive- or negative-ion HR-ESI-TOF-MS data were measured using a Bruker microTOF-QII mass spectrometer (Bruker, Karlsruhe, Germany). Analytical HPLC was carried out on a Shimadzu LC-16 instrument, and UV detection was carried out using a YMC-Pack ODS-A C18 (4.6 × 250 mm, 5 μm) column. All samples were purified by preparative HPLC using a Shimadzu HPLC system equipped with a UV detector and a Cosmosil 5C_{18}-MS-II column (20 × 250 mm, 5 μm, Nacalai Tesque, Inc., Nijo Karasuma, Japan). Silica gel (100–200, 200–300, and 300–400 mesh, Qingdao Marine Chemical Factory, Qingdao, China), ODS (50 μm, ODS-A-HG, YMC Co. ltd., Japan), and Sephadex LH-20 (GE Healthcare Bio-Sciences AB, Sweden) were used for open column chromatography (CC) to separate samples, and thin-layer chromatography (TLC) analysis were carried out using precoated silica gel GF_{254} plates. Solvents were of analytical grade (Guanghua Chemical Co., ltd. Guangzhou, P.R. China) for open CC and HPLC grade (Merck, Germany) for HPLC analysis.

2.2. Plant material

The dried aerial parts of *A. capillaris* Thunb. were gathered in Ganzhou, Jiangxi Province, China, in August 2019 and authenticated by Dr. Xiaobin Zeng of Shenzhen People's Hospital. A voucher specimen (No. 20190805) has been deposited in the Center Lab of Longhua Branch, Shenzhen People's Hospital, Second Clinical Medical College of Jinan University, Shenzhen, China.

2.3. Extraction and isolation

The air-dried aerial parts of *A. capillaris* (7.0 kg) were powered and extracted four times (5 days each) using 80 % EtOH at room temperature. A dark-brown crude extract (1.4 kg, 20 %) was afforded following concentration under reduced pressure. The extract was suspended in water (2 L) and partitioned successively with petroleum ether, ethyl acetate, and *n*-BuOH. The ethyl acetate fraction (114 g) was separated by ODS column chromatography, eluted with a MeOH − H_2O (5–100 %) gradient, and yielded ten fractions. Various column chromatographic separations of the 10 fractions afforded compounds **1**–**35**. The *n*-BuOH fraction (200 g) was first separated by silina gel column chromatography, eluted with a CH_2Cl_2-MeOH (5–100 %) gradient, and yielded six fractions. Various column chromatographic separations of FB. 3 afforded compounds **36**–**38**. Fig. 2 shows the extraction and isolation procedures for compounds from the aerial parts of *A. capillaris*. The purity of these compounds was determined as to be more than 95 % by HPLC.

2.3.1. Protocatechuic acid (1)

Pale yellow, oil; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 7.33 (1H, s, H-2), 7.28 (1H, d, J = 8.0 Hz, H-6), 6.78 (1H, d, J = 8.0 Hz,

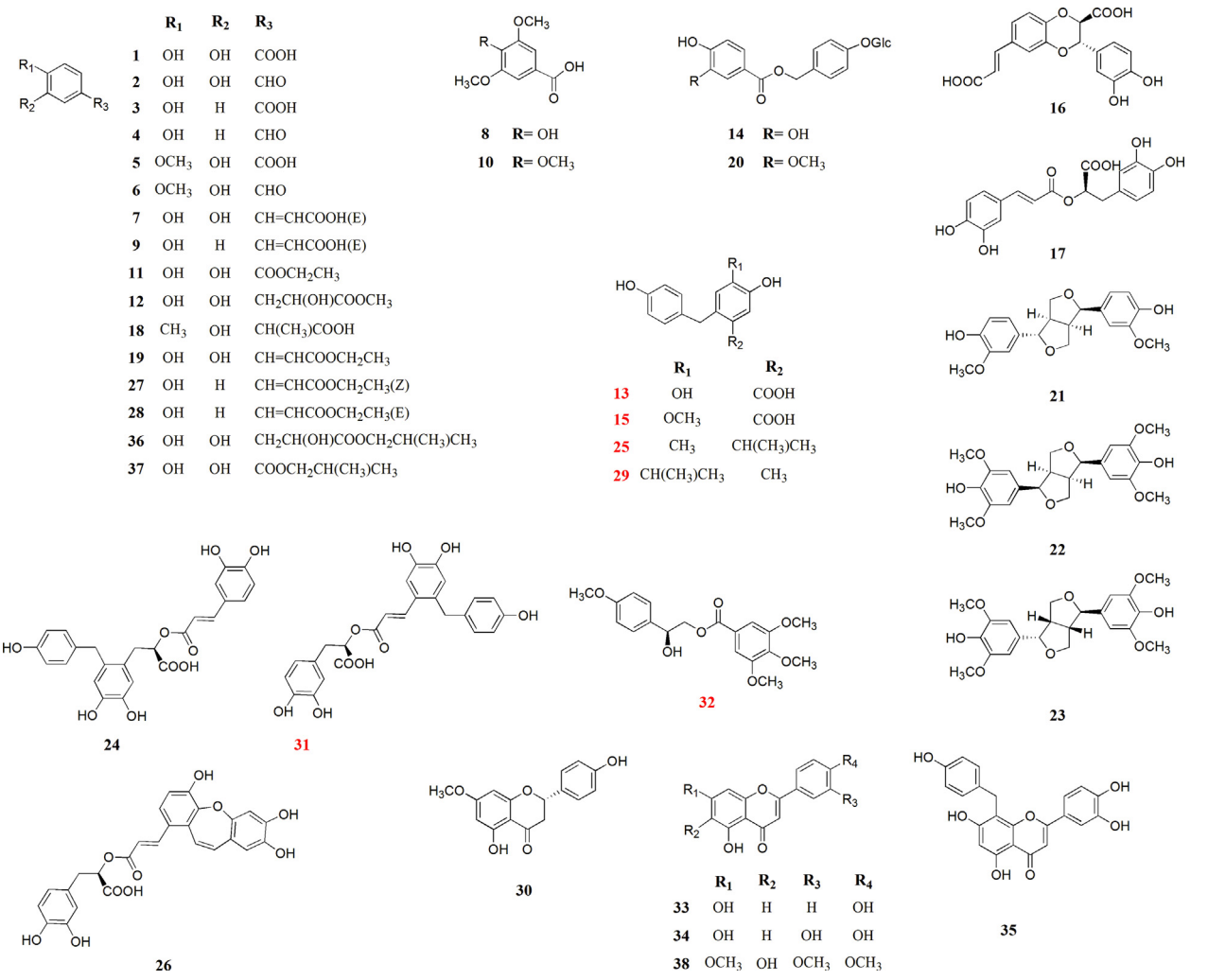


Fig. 1 Chemical structure of all compounds (**1**–**38**) from *A. capillaris* aerial parts.

H-5); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 167.3 (C-7), 150.0 (C-3), 144.9 (C-4), 121.9 (C-1), 121.7 (C-6), 116.6 (C-2), 115.2 (C-5).

2.3.2. Protocatechuyl aldehyde (2)

Pale yellow, oil; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 9.70 (1H, s, H-7), 7.26 (1H, d, J = 8.0 Hz, H-6), 7.23 (1H, s, H-2), 6.91 (1H, d, J = 8.0 Hz, H-5); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 191.1 (C-7), 152.1 (C-3), 145.9 (C-4), 128.8 (C-1), 124.5 (C-6), 115.5 (C-2), 114.4 (C-5).

2.3.3. 4-Hydroxybenzoic acid (3)

Pale yellow, oil; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 7.78 (2H, d, J = 7.1 Hz, H-2/6), 6.82 (2H, d, J = 7.1 Hz, H-3/5); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 167.2 (C-7), 161.6 (C-4), 131.5 (C-2/6), 121.4 (C-1), 115.1 (C-3/5).

2.3.4. 4-Hydroxybenzaldehyde (4)

Pale yellow, oil; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 7.75 (2H, d, J = 8.0 Hz, H-2/6), 6.92 (2H, d, J = 8.0 Hz, H-3/5); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 190.9 (C-7), 163.3 (C-4), 132.1 (C-2/6), 128.4 (C-1), 115.8 (C-3/5).

2.3.5. 3-Hydroxy-4-Methoxybenzoic acid (5)

Pale yellow, oil; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 7.43 (1H, d, J = 8.0 Hz, H-6),7.42 (1H, s, H-2), 6.84 (1H, d, J = 8.0 Hz, H-5), 3.80 (3H, s, H-OCH$_3$); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 167.2 (C-7), 151.1 (C-3), 147.2 (C-4), 123.5 (C-1), 121.6 (C-6), 115.0 (C-2), 112.7 (C-5), 55.5 (C-OCH$_3$).

2.3.6. 3-Hydroxy-4-Methoxy-Benzaldehyde (6)

Pale yellow, oil; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 7.41 (1H, d, J = 8.0 Hz, H-6),7.35 (1H, s, H-2), 6.98 (1H, d, J = 8.0 Hz, H-5), 3.82 (3H, s, H-OCH$_3$).

2.3.7. Caffeic acid (7)

Pale yellow, oil; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 7.39 (1H, d, J = 15.9 Hz, H-7),7.01 (1H, s, H-2), 6.95 (1H, d, J = 8.0 Hz, H-6), 6.75 (1H, d, J = 8.0 Hz, H-5), 6.16 (1H, d, J = 15.9 Hz, H-8); ^{13}C NMR (100 MHz, DMSO d_6) δ_C:

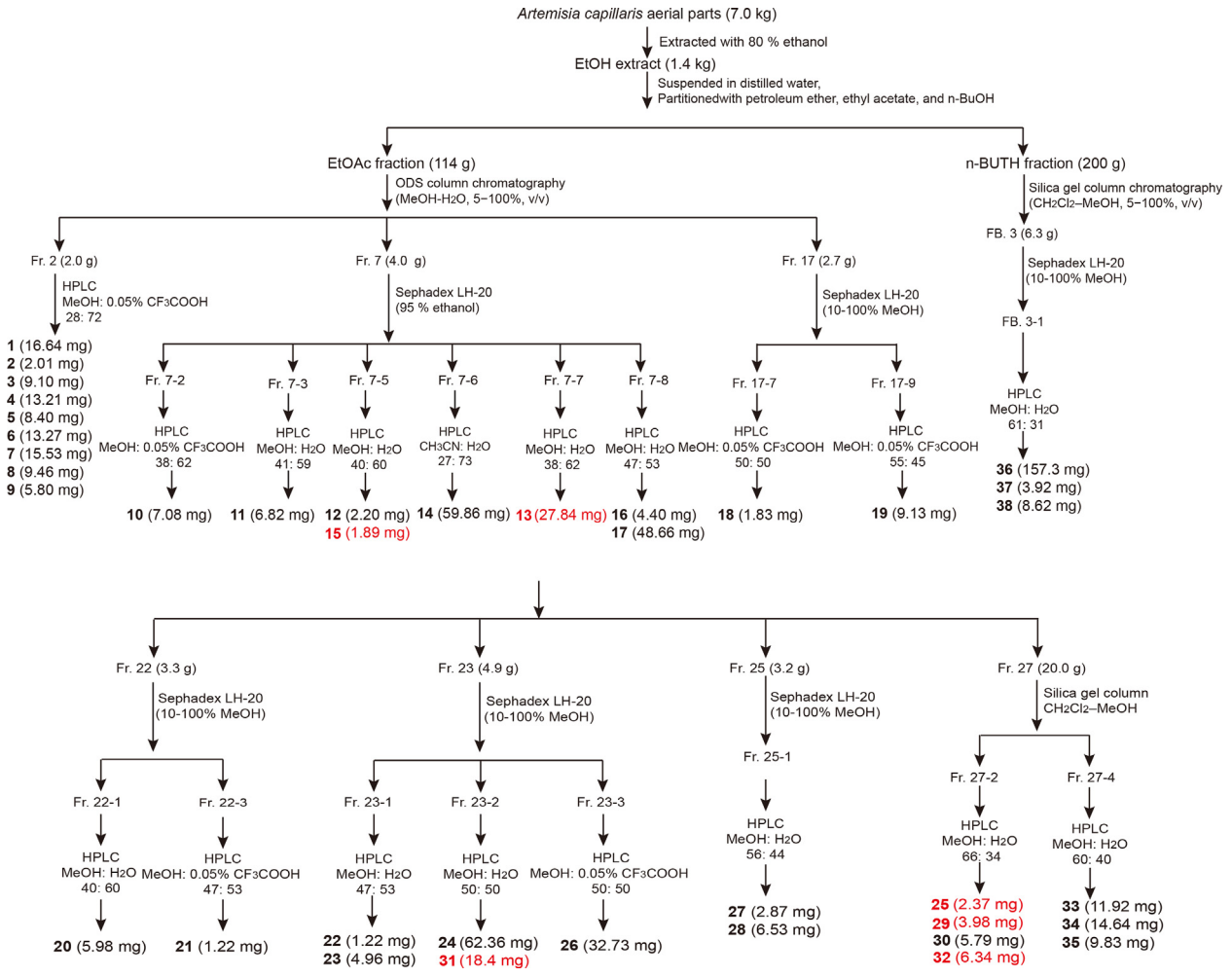


Fig. 2 Extraction and isolation procedure of compounds from *A. capillaris* aerial parts.

167.9 (C-9), 148.1 (C-3), 145.6 (C-4), 144.6 (C-7), 125.7 (C-1), 121.1 (C-6), 115.7 (C-2), 115.1 (C-5), 114.6 (C-8).

2.3.8. 3,5-Dimethoxy-4-Hydroxybenzoic acid (8)

Pale yellow, oil; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 7.20 (2H, s, H-2, 6), 3.80 (6H, s, 3,5-OCH$_3$); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 167.3 (C-7), 150.0 (C-3), 144.9 (C-4), 121.9 (C-1), 121.7 (C-6), 116.6 (C-2), 115.2 (C-5).

2.3.9. Cumaric acid (9)

Pale yellow, oil; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 7.51 (2H, d, J = 8.0 Hz, H-2, 6), 7.49 (1H, d, J = 15.9 Hz, H-7), 6.79 (2H, d, J = 8.0 Hz, H-3, 5), 6.28 (1H, d, J = 15.9 Hz, H-8).

2.3.10. 3,4,5-Trimethoxybenzoic acid (10)

Pale yellow, oil; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 7.23 (2H, s, H-2/6), 3.82 (6H, s, H$_3$-8/10), 3.72 (3H, s, H$_3$-9); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 166.9 (C-7), 152.7 (C-3/5), 141.4 (C-4), 125.9 (C-1), 106.6 (C-2/6), 60.1 (C-9), 56.0 (C-8/10).

2.3.11. 3,4-Dihydroxybenzoic acid ethyl ester (11)

Pale yellow, oil; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 7.37 (1H, s, H-2), 7.29 (1H, d, J = 8.0 Hz, H-6), 684 (1H, d, J = 8.0 Hz, H-5), 4.22 (2H, q, J = 7.0 Hz, H-8), 1.27 (3H, t, J = 7.0 Hz, H-9); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 165.7 (C-7), 150.4 (C-3), 145.1 (C-4), 121.6 (C-1), 120.7 (C-6), 116.3 (C-2), 115.4 (C-5), 60.0 (C-8), 14.3 (C-9).

2.3.12. 3,4,α-Trihydroxymethyl phenylpropionate (12)

Pale yellow, oil; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 6.59 (1H, d, J = 7.6 Hz, H-5), 6.58 (1H, d, J = 1.7 Hz, H-2), 6.42 (1H, dd, J = 7.6, 1.7 Hz, H-6), 4.11 (1H, dd, J = 7.7, 5.3 Hz, H-8), 3.59 (3H, s, H$_3$-10), 2.74 (1H, dd, J = 13.7, 5.3 Hz, H-7a), 2.67 (1H, dd, J = 13.7, 7.7 Hz, H-7b); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 174.0 (C-9), 144.8 (C-3), 143.7 (C-4), 128.2 (C-1), 120.0 (C-6), 116.7 (C-2), 115.2 (C-5), 71.7 (C-8), 51.3 (C-10), 39.7 (C-7).

2.3.13. Capillarisenol a (13)

Pale yellow, amorphous powder; UV (MeOH) λ^{max} (logε) 220, 261, and 297 nm; HR-ESI-TOF-MS m/z 283.0653 $[M + Na]^+$; IR ν_{max} 3386, 1656, 1514, 1027, 955 cm^{-1}; ^{1}H NMR (400 MHz, DMSO d_6) and ^{13}C NMR (100 MHz,DMSO d_6) spectrum information, see Table 1.

2.3.14. Amburoside a (14)

Pale yellow, oil; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 7.37 (2H, d, J = 8.3 Hz, H-2/6), 7.36 (1H, d, J = 2.0 Hz, H-2′), 7.33

Table 1 ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectroscopic data of compounds **13** and **15** in DMSO d_6 (δ in ppm, J in Hz).

No.	13		15	
	δ_H	δ_C	δ_H	δ_C
1	–	121.6	–	120.0
2	–	135.3	–	135.8
3	6.77, s	114.6	6.52, s	118.2
4	–	150.4	–	148.9
5	–	144.0	–	142.8
6	7.30, s	117.6	7.31, s	118.1
7	–	168.1	–	168.3
8	3.75, s	55.5	–	–
1′	–	132.0	–	132.0
2′	6.93, d (8.2 Hz)	129.4	6.91, d (8.2 Hz)	129.6
3′	6.61, d (8.2 Hz)	114.9	6.63, d (8.2 Hz)	115.0
4′	–	155.2	–	155.3
5′	6.61, d (8.2 Hz)	114.9	6.63, d (8.2 Hz)	115.0
6′	6.93, d (8.2 Hz)	129.4	6.91, d (8.2 Hz)	129.6
7′	4.16, s	37.3	4.10, s	37.1

(1H, dd, J = 8.2, 2.0 Hz, H-6′), 7.05 (2H, d, J = 8.3 Hz, H-3/5), 6.80 (1H, d, J = 8.2 Hz, H-5′), 5.19 (2H, s, H_2-7), 4.88 (1H, d, J = 7.3 Hz, H-1′’), 3.69 (1H, br d, J = 11.7 Hz, H-6′’a), 3.46 (1H, dd, J = 11.7, 5.7 Hz, H-6′’b), 3.33 (1H, m, H-5′’), 3.26 (2H, t, J = 9.0 Hz, H-2′’/3′’), 3.17 (1H, t, J = 9.0 Hz, H-4′’); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 165.6 (C-7′), 157.3 (C-4), 150.5 (C-4′), 145.1 (C-3′), 129.7 (C-1), 129.6 (C-2/C-6), 121.9 (C-6′), 120.6 (C-1′), 116.3 (C-2′), 116.2 (C-3/C-5), 115.4 (C-5′), 100.3 (C-1′’), 77.1 (C-3′’), 76.7 (C-5′’), 73.3 (C-2′’), 69.8 (C-4′’), 65.4 (C-7), 60.7 (C-6′’).

2.3.15. Capillarisenol b (15)

Pale yellow, amorphous powder; UV (MeOH) λ^{max} (logε) 222, 259, and 296 nm; HR-ESI-TOF-MS m/z 274.2749 $[M + H]^+$; IR ν_{max} 3436, 1655, 1438, 1027, 955 cm^{-1}; ^{1}H NMR (400 MHz, DMSO d_6) and ^{13}C NMR (100 MHz,DMSO d_6) spectrum information, see Table 1.

2.3.16. Trans-6-[(1E)-2-Carboxyethenyl]-3-(3,4-Hihydroxyphenyl)-2,3- Dihydro-1,4-Benzodioxin-2-Carboxlic acid (16)

Yellow, oil; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 7.48 (1H, d, J = 15.9 Hz, H-7′), 7.29 (1H, d, J = 2.0 Hz, H-2′), 7.20 (1H, dd, J = 2.0, 8.0 Hz, H-5′), 6.95 (1H, d, J = 8.0 Hz, H-6′), 6.80 (1H, s, H-2), 6.70 (2H, s, H-5, 6), 6.37 (1H, d, J = 15.9 Hz, H-8′), 5.26 (1H, d, J = 4.3 Hz, H-7), 5.09 (1H, d, J = 4.4 Hz, H-8); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 168.9 (C-9), 167.7 (C-9′), 145.7 (C-4), 145.2 (C-3), 144.0 (C-3′), 143.5 (C-7′), 142.3 (C-4′), 128.1 (C-1), 126.7 (C-1′), 122.3 (C-6′), 118.4 (C-6), 117.4 (C-5′), 117.1 (C-8′), 116.7 (C-2′), 115.4 (C-2), 114.6 (C-5′), 75.1 (C-8), 74.6 (C-7).

2.3.17. Rosmarinic acid (17)

Yellow, oil; ^{1}H NMR (400 MHz, DMSO d_6) and ^{13}C NMR (100 MHz,DMSO d_6) spectrum information, see Table 2.

2.3.18. 2-(3-Hydroxy-4-Methylphenyl)Propanoic acid (18)

Yellow, oil; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 6.96 (1H, d, J = 7.6 Hz, H-6), 6.70 (1H, d, J = 1.7 Hz, H-3), 6.59 (1H, dd, J = 7.6, 1.7 Hz, H-5), 3.49 (1H, q, J = 7.1 Hz, H-8), 2.06 (3H, s, H_3-7), 1.28 (3H, d, J = 7.1 Hz, H_3-9); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 175.6 (C-10), 155.3 (C-2), 139.8 (C-4), 130.4 (C-6), 122.2 (C-1), 117.9 (C-5), 113.4 (C-3), 44.4 (C-8), 18.6 (C-9), 15.6 (C-7).

2.3.19. Caffeic acid ethyl ester (19)

Yellow, oil; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 7.46 (1H, d, J = 15.9 Hz, H-7), 7.04 (1H, d, J = 2.0 Hz, H-2), 6.99 (1H, dd, J = 8.1, 2.0 Hz, H-6), 6.76 (1H, d, J = 8.1 Hz, H-5), 6.25 (1H, d, J = 15.9 Hz, H-8), 4.15 (2H, q, J = 7.1 Hz, H_2-1′), 1.24 (3H, t, J = 7.1 Hz, H_3-2′); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 166.5 (C-9), 148.4 (C-4), 145.6 (C-7), 145.0 (C-3), 125.5 (C-1), 121.3 (C-6), 115.7 (C-5), 114.8 (C-2), 114.0 (C-8), 59.7 (C-1′), 14.3 (C-2′).

2.3.20. Amburoside b (20)

Yellow, amorphous powder; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 7.44 (1H, dd, J = 8.5, 2.1 Hz, H-6′), 7.38 (2H, d, J = 8.6 Hz, H-2/6), 7.37 (1H, d, J = 2.1 Hz, H-2′), 7.04 (2H, d, J = 8.6 Hz, H-3/5), 7.01 (1H, d, J = 8.5 Hz, H-5′), 5.21 (2H, s, H_2-7), 4.87 (1H, d, J = 7.2 Hz, H-1′’), 3.82 (3H, s, H_3-8′), 3.69 (1H, br d, J = 11.6 Hz, H-6′’a), 3.45 (1H, dd, J = 11.7, 5.7 Hz, H-6′’b), 3.33 (1H, m, H-5′’), 3.25 (2H, t, J = 8.2 Hz, H-2′’/3′’), 3.17 (1H, t, J = 8.2 Hz, H-4′’); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 165.4 (C-7′), 157.3 (C-4), 152.0 (C-4′), 146.3 (C-3′), 129.7 (C-2/C-6), 129.6 (C-1), 121.9 (C-6′), 121.6 (C-1′), 116.2 (C-3/C-5), 115.7 (C-5′), 111.5 (C-2′), 100.3 (C-1′’), 77.1 (C-3′’), 76.6 (C-5′’), 73.2 (C-2′’), 69.7 (C-4′’), 65.6 (C-7), 60.7 (C-6′’), 55.7 (C-8′).

2.3.21. (+)-Epi-Pinoresinol (21)

Yellow amorphous solid; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 8.85 (1H, s, OH), 8.81 (1H, s, OH), 6.90 (2H, s, H-2′’/2′), 6.75 (4H, overlapped, H-5′/5′’/6′’/6′), 4.77 (1H, d, J = 5.9 Hz, H-2), 4.32 (1H, d, J = 6.8 Hz, H-6), 4.05 (1H, d, J = 9.2 Hz, H-4ex), 3.77 (6H, s, OCH_3 × 2), 3.73 (2H, overlapped, H-8ex, 4ax), 3.38 (1H, overlapped, H-8ax), 3.10 (1H, t, J = 8.5 Hz, H-1), 2.83 (1H, q, J = 7.1 Hz, H-5); ^{13}C NMR (100 MHz,

Table 2 ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectroscopic data of compounds **17** (Rosmarinic acid), **24** and **31** in DMSO d_6 (δ in ppm, J in Hz).

No.	**17** (Rosmarinic acid)		**24**		**31**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	–	125.4	–	125.4	–	123.0
2	7.09, d (2.1 Hz)	114.9	7.07, br s	115.0	7.10, s	113.1
3	–	145.5	–	145.7	–	144.2
4	–	148.6	–	148.7	–	148.6
5	6.79, d (8.1 Hz)	115.8	6.79, d (8.1 Hz)	115.9	6.60, s	117.6
6	7.02, dd (2.1, 8.1 Hz)	121.4	7.01, d (8.1 Hz)	121.7	–	133.9
7	7.49, d (15.9 Hz)	145.6	7.48, d (15.9 Hz)	146.0	7.80, d (15.7 Hz)	142.5
8	6.27, d (15.9 Hz)	113.6	6.24, d (15.9 Hz)	113.3	6.11, d (15.7 Hz)	114.0
9	–	166.0	–	166.0	–	166.0
1′	–	127.9	–	125.1	–	127.6
2′	6.71, d (2.1 Hz)	116.7	6.66, s	117.7	6.67, d (1.1 Hz)	116.6
3′	–	144.9	–	143.3	–	145.0
4′	–	143.9	–	143.9	–	144.0
5′	6.67, d (8.1 Hz)	115.4	6.46, s	117.5	6.62, d (8.1 Hz)	115.4
6′	6.55, dd (2.1, 8.1 Hz)	119.9	–	131.3	6.49, d (1.1, 8.1 Hz)	120.1
7′	2.93, dd (8.2, 14.4 Hz); 3.01, dd (4.4, 14.4 Hz)	36.4	2.90, dd (9.2, 14.5 Hz); 3.03, dd (4.1, 14.5 Hz)	33.1	2.87, dd (8.7, 14.4 Hz); 2.98, dd (3.4, 14.4 Hz)	36.3
8′	5.06, dd (4.4, 8.2 Hz)	73.6	4.96, dd (4.1, 9.2 Hz)	72.9	4.98, dd (3.4, 8.7 Hz)	73.2
9′	–	171.3	–	171.2	–	171.0
1′’	–	–	–	130.6	–	131.1
2′’	–	–	6.91, d (8.3 Hz)	129.4	6.87, d (8.2 Hz)	129.2
3′’	–	–	6.67, d (8.3 Hz)	115.2	6.65, d (8.2 Hz)	115.2
4′’	–	–	–	155.4	–	155.4
5′’	–	–	6.67, d (8.3 Hz)	115.2	6.65, d (8.2 Hz)	115.2
6′’	–	–	6.91, d (8.3 Hz)	129.4	6.87, d (8.2 Hz)	129.2
7′’	–	–	3.78, s	36.5	3.81, s	36.4

DMSO d_6) δ_C: 147.5 (C-3′’), 147.3 (C-3′), 146.0 (C-4′’), 145.4 (C-4′), 132.3 (C-1′’), 129.6 (C-1′), 118.6 (C-6′’), 117.9 (C-6′), 115.1 (C-5′’/5′), 110.3 (C-2′’), 109.8 (C-2′), 87.0 (C-2), 81.4 (C-6), 70.3 (C-8), 68.8 (C-4), 55.6 (OCH_3 × 2), 53.9 (C-1), 49.4 (C-5).

2.3.22. (+)-Diasyringaresinol (22)

Yellow amorphous solid; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 8.25 (2H, s, OH × 2), 6.59 (4H, s, H-2′/6′/2′’/6′’), 4.82 (1H, d, J = 4.6 Hz, H-2/6), 3.75 (12H, s, OCH_3 × 4), 3.46 (4H, d, J = 3.6 Hz, H_2-4/8), 3.23 (2H, m, H-1/5); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 147.8 (C-3′/5′/3′’/5′’), 134.3 (C-4′/4′’), 129.3 (C-1′/1′’), 103.6 (C-2′/6′/2′’/6′’), 83.3 (C-2/6), 68.1 (C-4/8), 55.9 (OCH_3 × 4), 48.6 (C-1/5).

2.3.23. (+)-Lirioresinol a (23)

Yellow amorphous solid; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 8.26 (1H, s, OH), 8.23 (1H, s, OH), 6.61 (2H, s, H-2′’/6′’), 6.59 (2H, s, H-2′/6′), 4.76 (1H, d, J = 5.9 Hz, H-2), 4.32 (1H, d, J = 6.9 Hz, H-6), 4.09 (1H, d, J = 9.3 Hz, H-4ex), 3.77 (2H, overlapped, H-8ex, 4ax), 3.75 (12H, s, OCH_3 × 4), 3.38 (1H, overlapped, H-8ax), 3.10 (1H, t, J = 8.6 Hz, H-1), 2.83 (1H, q, J = 7.1 Hz, H-5); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 147.9 (C-3′’/5′’), 147.8 (C-3′/5′), 134.9 (C-1′’), 134.2 (C-4′’), 131.5 (C-4′), 128.8 (C-1′), 103.6 (C-2′’/6′’), 103.0 (C-2′/6′), 87.1 (C-6), 81.5 (C-2), 70.2 (C-4), 68.9 (C-8), 56.0 (OCH_3 × 4), 53.9 (C-5), 49.3 (C-1).

2.3.24. 2-Caffeoyloxy-3-[2-(4-Hydroxybenzyl)-4,5-Dihydroxy]Phenyl propionic acid (24)

Pale yellow, oil; HR-ESI-TOF-MS m/z 465.1054 $[M - H]^-$; ^{1}H NMR (400 MHz, DMSO d_6) and ^{13}C NMR (100 MHz, DMSO d_6) spectrum information, see Table 2.

2.3.25. Capillarisenol C (25)

Pale yellow, amorphous powder; UV (MeOH) λ^{max} (logε) 204, 225, and 279 nm; HR-ESI-TOF-MS m/z 255.1310 $[M - H]^-$; IR ν_{max} 3436, 1660, 1513, 1052, 955 cm^{-1}; ^{1}H NMR (400 MHz, DMSO d_6) and ^{13}C NMR (100 MHz,DMSO d_6) spectrum information, see Table 3.

2.3.26. Isosalvianolic acid C (26)

Yellow, oil; HR-ESI-TOF-MS m/z 491.0654 $[M - H]^-$; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 7.82 (1H, d, J = 15.7 Hz, H-15), 7.46 (1H, d, J = 8.4 Hz, H-11), 6.90 (1H, d, J = 8.4 Hz, H-12), 6.86 (2H, d, J = 4.8 Hz, H-7/8), 6.85 (1H, s, H-2), 6.69 (1H, d, J = 2.0 Hz, H-2′), 6.67 (1H, d, J = 8.0 Hz, H-5′), 6.65 (1H, s, H-5), 6.56 (1H, dd, J = 8.0, 2.0 Hz, H-6′), 6.33 (1H, d, J = 15.7 Hz, H-16), 5.05 (1H, dd, J = 8.2, 4.4 Hz, H-8′), 3.01 (1H, dd, J = 14.2, 4.4 Hz, H-7′b), 2.93 (1H, dd, J = 14.2, 8.2 Hz, H-7′a); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 170.7 (C-9′), 165.6 (C-17), 151.1 (C-13), 150.0 (C-4), 147.2 (C-1), 145.1 (C-14), 145.0 (C-3′), 144.1 (C-4′), 142.6 (C-3), 141.6 (C-15), 131.9 (C-7), 131.1 (C-9), 127.2 (C-1′), 124.3 (C-11), 123.2 (C-8), 122.5 (C-10), 121.0

Table 3 ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectroscopic data of compounds **25** and **29** in DMSO d_6 (δ in ppm, J in Hz).

No.	25		29	
	δ_H	δ_C	δ_H	δ_C
1	–	153.9	–	152.4
2	–	120.7	–	131.2
3	6.77, s	132.4	6.84, s	127.3
4	–	127.9	–	129.7
5	–	144.7	–	133.5
6	6.67, s	111.6	6.53, s	116.7
7	2.98, m	28.2	3.11, m	26.1
8	1.00, d (6.8 Hz)	23.8	1.11, d (6.9 Hz)	22.6
9	1.00, d (6.8 Hz)	23.8	1.11, d (6.9 Hz)	22.6
10	2.04, s	15.6	2.02, s	18.9
1′	–	132.0	–	131.3
2′	6.86, d (8.4 Hz)	129.1	6.87, d (8.4 Hz)	129.1
3′	6.64, d (8.4 Hz)	115.0	6.63, d (8.4 Hz)	115.0
4′	–	155.2	–	155.1
5′	6.64, d (8.4 Hz)	115.0	6.63, d (8.4 Hz)	115.0
6′	6.86, d (8.4 Hz)	129.1	6.87, d (8.4 Hz)	129.1
7′	3.73, s	36.5	3.68, s	37.4

(C-6), 120.1 (C-6′), 116.8 (C-12), 116.7 (C-2′), 116.2 (C-16), 115.4 (C-5), 114.5 (C-5′), 108.9 (C-2), 72.9 (C-8′), 36.1 (C-7′).

2.3.27. 2-cis-p-Hydroxyl ethyl cinnamate (27)

Yellow, oil; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 7.62 (2H, d, J = 8.7 Hz, H-2/6), 6.84 (1H, d, J = 12.8 Hz, H-7), 6.75 (2H, d, J = 8.7 Hz, H-3/5), 5.75 (1H, d, J = 12.8 Hz, H-8), 4.11 (2H, q, J = 7.1 Hz, H_2-1′), 1.20 (3H, t, J = 7.1 Hz, H_3-2′); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 166.0 (C-9), 158.8 (C-4), 143.0 (C-7), 132.5 (C-2/6), 125.5 (C-1), 115.6 (C-8), 114.9 (C-3/5), 59.6 (C-1′), 14.1 (C-2′).

2.3.28. trans-p-Hydroxyl ethyl cinnamate (28)

Yellow, oil; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 7.56 (1H, d, J = 15.9 Hz, H-7), 7.55 (2H, d, J = 8.3 Hz, H-2/6), 6.79 (2H, d, J = 8.3 Hz, H-3/5), 6.37 (1H, d, J = 15.9 Hz, H-8), 4.16 (2H, q, J = 7.0 Hz, H_2-1′), 1.24 (3H, t, J = 7.0 Hz, H_3-2′); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 166.6 (C-9), 159.9 (C-4), 144.6 (C-7), 130.3 (C-2/6), 125.1 (C-1), 115.8 (C-8), 114.3 (C-3/5), 59.7 (C-1′), 14.3 (C-2′).

2.3.29. Capillarisenol d (29)

Yellow, amorphous powder; UV (MeOH) λ^{max} (logε) 204, 226, and 279 nm; HR-ESI-TOF-MS m/z 255.1309 $[M - H]^-$; IR ν_{max} 3418, 1658, 1438, 1027, 954 cm^{-1}; ^{1}H NMR (400 MHz, DMSO d_6) and ^{13}C NMR (100 MHz,DMSO d_6) spectrum information, see Table 3.

2.3.30. Sakuranetin (30)

Yellow, amorphous powder; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 12.12 (1H, s, 5-OH), 9.61 (1H, s, 4′-OH), 7.33 (2H, d, J = 8.5 Hz, H-2′/6′), 6.80 (2H, d, J = 8.5 Hz, H-3′/5′), 6.11 (1H, d, J = 2.3 Hz, H-8), 6.08 (1H, d, J = 2.3 Hz, H-6), 5.49 (1H, dd, J = 12.8, 2.9 Hz, H-2), 3.79 (3H, s, H_3-11), 3.32 (1H, dd, J = 17.1, 12.8 Hz, H-3a), 2.73 (1H, dd, J = 17.1, 2.9 Hz, H-3b); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 197.0 (C-4), 167.4 (C-7), 163.2 (C-5), 162.9 (C-9), 157.8 (C-4′), 128.7 (C-1′), 128.4 (C-2′/6′), 115.1 (C-3′/5′), 102.6 (C-10), 94.6 (C-6), 93.8 (C-8), 78.6 (C-2), 55.9 (C-11), 42.0 (C-3).

2.3.31. Capillarisenol E (31)

Pale yellow, amorphous powder; $[\alpha]_D^{25}$ + 76.7° (c = 1.5, MeOH); UV (MeOH) λ^{max} (logε) 215 and 267 nm; HR-ESI-TOF-MS m/z 465.1051 $[M - H]^-$; IR ν_{max} 3436, 1660, 1437, 1050, 955 cm^{-1}; ^{1}H NMR (400 MHz, DMSO d_6) and ^{13}C NMR (100 MHz,DMSO d_6) spectrum information, see Table 2.

2.3.32. (7′S)-2-Hydroxy-2-(4-Methoxyphenyl)Ethyl3,4,5-Trimethoxy benzoate (32)

Pale yellow, amorphous powder; $[\alpha]_D^{25}$ −4.6° (c = 1.0, MeOH); UV (MeOH) λ^{max} (logε) 215 and 267 nm; HR-ESI-TOF-MS m/z 385.1203 $[M + Na]^+$; IR ν_{max} 3445, 1660, 1438, 1028, 955 cm^{-1}; ^{1}H NMR (400 MHz, DMSO d_6) and ^{13}C NMR (100 MHz,DMSO d_6) spectrum information, see Table 4.

2.3.33. Luteolin (33)

Yellow, amorphous powder; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 12.97 (1H, s, 5-OH), 7.41 (1H, dd, J = 8.1, 1.8 Hz, H-6′), 7.40 (1H, d, J = 1.8 Hz, H-2′), 6.89 (1H, d, J = 8.1 Hz, H-5′), 6.66 (1H, s, H-3), 6.45 (1H, d, J = 2.0 Hz, H-8), 6.19 (1H, d, J = 2.0 Hz, H-6); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 181.6 (C-4), 164.1 (C-2), 163.9 (C-7), 161.4 (C-5), 157.3 (C-9), 149.7 (C-3′), 145.7 (C-4′), 121.5 (C-1′), 119.0 (C-6′), 116.0 (C-5′), 113.4 (C-2′), 103.7 (C-10), 102.8 (C-3), 98.8 (C-6), 93.8 (C-8).

2.3.34. Apigenin (34)

Yellow, amorphous powder; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 12.96 (1H, s, 5-OH), 7.92 (2H, d, J = 8.7 Hz, H-2′/6′), 6.92 (2H, d, J = 8.7 Hz, H-3′/5′), 6.78 (1H, s, H-3), 6.48 (1H, d, J = 2.1 Hz, H-8), 6.19 (1H, d, J = 2.1 Hz, H-6); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 181.7 (C-4), 164.1 (C-2), 163.7 (C-7), 161.4 (C-5), 161.2 (C-4′), 157.3 (C-9), 128.5 (C-2′/6′),

Table 4 ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectroscopic data of compound **32** in DMSO d_6 (δ in ppm, J in Hz).

No.	32	
	δ_H	δ_C
1	–	124.8
2	7.20, s	106.5
3	–	152.7
4	–	141.7
5	–	152.7
6	7.20, s	106.5
7	–	165.1
8	3.81, s	56.0
9	3.73, s	60.2
10	3.81, s	56.0
1′	–	134.0
2′	7.37, d (8.5 Hz)	127.5
3′	6.92, d (8.5 Hz)	113.5
4′	–	158.6
5′	6.92, d (8.5 Hz)	113.5
6′	7.37, d (8.5 Hz)	127.5
7′	4.88, m	69.8
8′	4.25, m	69.4
9′	3.74, s	55.4

121.2 (C-1′), 116.0 (C-3′/5′), 103.7 (C-10), 102.8 (C-3), 98.8 (C-6), 94.0 (C-8).

2.3.35. C-p-Hydroxybenzylluteolin (35)

Yellow, oil; HR-ESI-TOF-MS m/z 391.0544 $[M - H]^-$; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 12.95 (1H, s, 5-OH), 7.43 (1H, d, J = 2.2 Hz, H-2′), 7.35 (1H, dd, J = 8.2, 2.2 Hz, H-6′), 7.06 (2H, d, J = 8.1 Hz, H-2″/6″), 6.88 (1H, d, J = 8.2 Hz, H-5′), 6.67 (1H, s, H-3), 6.60 (2H, d, J = 8.1 Hz, H-3″/5″), 6.32 (1H, s, H-6), 3.98 (1H, s, H_3-7″); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 182.4 (C-4), 164.2 (C-2), 162.3 (C-7), 159.7 (C-5), 155.8 (C-4″), 154.9 (C-9), 150.1 (C-4′), 146.2 (C-3′), 131.2 (C-1″), 129.4 (C-2″/6″), 122.2 (C-1′), 119.3 (C-6′), 116.5 (C-5′), 115.4 (C-3″/5″), 113.8 (C-2′), 107.1 (C-8), 104.1 (C-10), 103.0 (C-3), 98.9 (C-6), 27.4 (C-7″).

2.3.36. 3,4,α-Trihydroxy-Isobutylphenylpropionate (36)

Yellow, oil; HR-ESI-TOF-MS m/z 253.1135 $[M - H]^-$; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 6.63 (1H, d, J = 8.1 Hz, H-5), 6.62 (1H, d, J = 2.1 Hz, H-2), 6.45 (1H, dd, J = 8.1, 2.1 Hz, H-6), 4.17 (1H, dd, J = 7.4, 5.6 Hz, H-8), 3.79 (2H, d, J = 6.6 Hz, H_2-10), 2.78 (1H, dd, J = 13.7, 5.6 Hz, H-7a), 2.69 (1H, dd, J = 13.7, 7.4 Hz, H-7b), 1.82 (1H, m, H-11), 0.83 (6H, d, J = 6.6 Hz, H_3-12/H_3-13); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 174.0 (C-9), 145.1 (C-3), 144.0 (C-4), 128.6 (C-1), 120.4 (C-6), 117.1 (C-2), 115.6 (C-5), 72.1 (C-8), 70.2 (C-10), 40.1 (C-7), 27.6 (C-11), 19.1 (C-12/13).

2.3.37. Isobutyl protocatechuate (37)

Yellow, oil; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 7.37 (1H, d, J = 2.1 Hz, H-2), 7.32 (1H, dd, J = 8.2, 2.1 Hz, H-6), 6.81 (1H, d, J = 8.2 Hz, H-5), 3.97 (2H, d, J = 6.5 Hz, H_2-8), 1.98 (1H, m, H-9), 0.95 (6H, d, J = 6.5 Hz, H_3-10/H_3-11); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 165.7 (C-7), 150.4 (C-3), 145.1 (C-4), 121.7 (C-1), 120.7 (C-6), 116.2 (C-2), 115.4 (C-5), 69.8 (C-8), 27.5 (C-9), 19.0 (C-10/11).

2.3.38. 5,6-Dihydroxy-7,3′,4′-Trimethoxyflavone (38)

Yellow, amorphous powder; ^{1}H NMR (400 MHz, DMSO d_6) δ_H: 7.54 (1H, s, H-3), 7.02 (1H, s, H-4), 7.01 (1H, s, H-7), 4.05 (2H, d, J = 6.6 Hz, H_2-9), 2.00 (1H, m, H-10), 0.95 (6H, d, J = 6.6 Hz, H_3-11/H_3-12); ^{13}C NMR (100 MHz, DMSO d_6) δ_C: 158.8 (C-8), 150.3 (C-7a), 148.2 (C-6), 144.1 (C-5), 143.1 (C-2), 118.1 (C-3a), 114.7 (C-3), 106.0 (C-4), 97.8 (C-7), 70.2 (C-9), 27.4 (C-10), 18.9 (C-11/12).

2.4. Anti-Hepatoma activity assay in vitro

Huh 7 cells and HepG 2 cells were maintained in DMEM containing 10 % FBS (foetal bovine serum) and cultured at 37 °C (5 % CO_2, 95 % relative humidity). A cytotoxicity assay was performed, according to the CCK8 method, using 96-well microplates. Briefly, 200 μL of adherent cells were seeded into each well of the 96-well cell culture plates and allowed to adhere for 24 h before drug addiction, with an initial density of 5×10^3 cells each well. Each tumor cell line was exposed to the test compounds at different concentrations for six times within 48 h.

3. Results and discussion

3.1. Structural elucidation of five new bisphenols (13, 15, 25, 29, 31)

Compound **13** was isolated as white amorphous powder. Its molecular formula was determined as $C_{14}H_{12}O_5$ by the HR-ESI-TOF-MS at m/z 283.0653 $[M + Na]^+$. The UV maximum absorptions at 220, 261, and 297 nm indicated the existence of aromatic moieties. In the ^{1}H NMR spectrum of **13**, characteristic signals corresponding to a 1,2,4,5-tetrasubstituted benzene ring [δ_H 6.52 (s, H-3) and 7.31 (s, H-6)], a 1,4-disubstituted benzene ring [δ_H 6.91 (2H, d, J = 8.2 Hz, H-2′/H-6′) and 6.63 (2H, d, J = 8.2 Hz, H-3′/H-5′)], and methylene [δ_H 4.10 (2H, s, H_2-7′)] were observed. The ^{13}C NMR spectrum of **13** revealed the presence of 14 carbon signals, which were assigned based on the DEPT-135 spectrum to a carbonyl group [δ_C 168.3 (C-7)], eight aromatic carbons [δ_C 120.0 (C-1), 135.8 (C-2), 118.2 (C-3), 148.9 (C-4), 142.8 (C-5), 118.1 (C-6), 132.0 (C-1′), 129.6 (C-2′/C-6′), 115.0 (C-3′/C-5′), and 155.3 (C-4′)], and a methylene carbon [δ_C 37.1 (C-7′)]. Based on the comprehensive analysis of ^{1}H–^{1}H COSY, HSQC, and HMBC spectra, the ^{1}H and ^{13}C NMR spectral data of **13** were assigned (Table 1).

Interpretation of the ^{1}H–^{1}H COSY correlations (Fig. 3) led to the assignment of two spin-coupling systems (H-2′ to H-3′ and H-5′ to H-6′) in **13**. In the HMBC spectrum, correlations between H-3 and C-1/C-5/C-7′, as well as between H-6 and C-2/C-4/C-7, allowed the establishment of a 1,2,4,5-tetrasubstituted benzene ring moiety (**a**), in which C-4 and C-5 were oxygenated due to its obvious downfield shift (δ_C 148.9 and 142.8). Meanwhile, HMBC correlations between H-2′/H-6′ and C-4′ and between H-3′/H-5′ and C-1′, in which C-4′ was oxygenated due to its obvious downfield shift (δ_C 155.3), indicated the existence of a *p*-hydroxybenzene unit

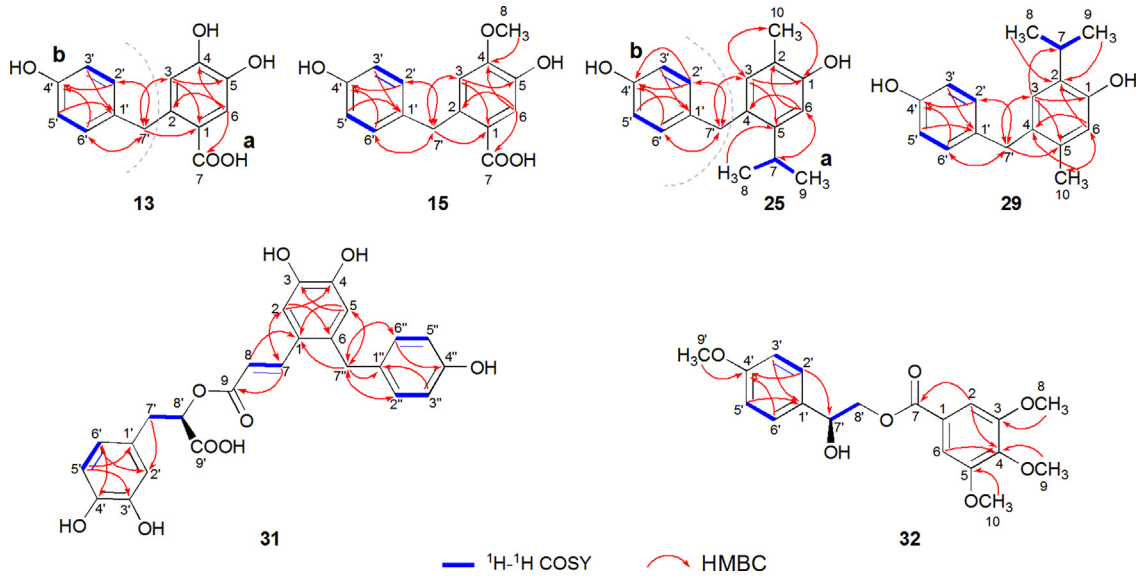


Fig. 3 Key ^{1}H–^{1}H COSY, HMBC and NOESY correlations of five new bisphenols (**13**, **15**, **25**, **29**, **31**) and one new aromatic compound **32**.

(**b**). Furthermore, the HMBC correlations between H-3/H-2′/H-6′ and C-7′ as well as between H_2-7′ and C-1/C-3/C-2′/C-6′ implied that two fragments (**a** and **b**) were connected by methylene (C-2 − C-7′−C-1′ bond). Moreover, the remaining carbonyl and hydroxyl groups could be assigned to a carboxyl moiety based on molecular formula information, and this moiety was attached to the C-1 position on the basis of the HMBC correlation between H-6 and C-7. Hence, the planar structure of **13** was confirmed (Fig. 3) by the analysis, and compound **13** was identified as 2-*C*-*p*-hydroxybenzylprotocatechuic acid, which was renamed capillarisenol A.

Compound **15** was obtained as an off-white amorphous powder. Its molecular formula was determined to be $C_{15}H_{14}O_5$ according to the HR-ESI-TOF-MS data at *m*/*z* 274.2749 $[M + H]^+$. The UV spectrum of **15** showed the absorption maxima at 222, 259, and 296 nm. In the ^{1}H and ^{13}C NMR spectra of **15**, a 1,2,4,5-tetrasubstituted aromatic fragment, a 1,4-disubstituted aromatic fragment, a carboxyl group, a methylene, and a methoxyl group were observed. Extensive analysis of the 1D- and 2D NMR data (Table 1) of **15** indicated that its skeletal structure was identical to that of **13**, and the difference between them is that the hydroxyl group (δ_C 148.9, C-4) in **13** was replaced by a methoxyl group (δ_C 150.4, C-4; δ_C 55.5, C-8) in **15**, which was supported by the HMBC correlations from H_3-8 (s, δ_H 3.75) to C-4 (Fig. 2). Accordingly, compound **15** was determined to be 2-*C*-*p*-hydroxybenzylisovanillic acid, which was renamed capillarisenol B.

Compound **25** was isolated as yellow oil. Its molecular formula was established as $C_{17}H_{20}O_2$ based on its negative HR-ESI-TOF-MS data (*m*/*z* 255.1310 $[M - H]^-$). The UV maximum absorptions at 204, 225, and 279 nm supported the presence of aromatic moieties. The ^{1}H NMR spectrum of DMSO d_6 indicated a 1,2,4,5-tetrasubstituted benzene ring due to the presence of two aromatic proton singlets at δ 6.67 (1H, s) and 6.77 (1H, s) and a 1,4-disubstituted benzene ring due to aromatic protons at δ 6.86 (2H, d, J = 8.4 Hz) and 6.64 (2H, d, J = 8.4 Hz), one two-proton singlet at δ 3.73 (2H, s), and one three-proton singlet at δ 2.04 (3H, s) assignable to the methylene and methyl groups likely attached to the aromatic ring, respectively, as well as two overlapping three-proton doublets at δ 1.00 (6H, d), assignable to two methyl groups likely attached to the methine group. Furthermore, the 17 carbons were resolved as 14 carbon signals in the ^{13}C NMR, confirming the presence of structurally symmetric subunits in the compound. Based on 1D- and 2D NMR experiments, the ^{1}H- and ^{13}C NMR data of **25** were assigned and listed (Table 3).

The ^{1}H–^{1}H COSY correlations led to the establishment of three spin-coupling systems in **25**, as shown in blue bold lines in Fig. 3. In the HMBC spectrum, key correlations between H-3 and C-1/C-10, between H-6 and C-2/C-4/C-7, between H-7 and C-6, between H_3-8/H_3-9 and C-5, and between H_3-10 and C-1/C-3 established a carvacrol motif (**a**). In addition, the HMBC correlations between H-2′/H-6′ and C-4′ and between H-3′/H-5′ and C-1′ suggested the existence of an *p*-hydroxybenzene unit (**b**), in which C-4′ was oxygenated due to its obvious downfield shift (δ 155.2). Furthermore, the HMBC correlations between H-3/H-6′ and C-7′ as well as between H_2-7′ and C-2′/C-6′ implied that two substructures (**a** and **b**) were also connected through the C-4 − C-7′−C-1′ bond. Consequently, compound **25** was identified as 4-*C*-*p*-hydroxybenzylcarvacrol, which was renamed capillarisenol C.

The molecular formula of compound **29** was determined to be $C_{17}H_{20}O_2$ based on HR-ESI-TOF-MS analysis (*m*/*z* 255.1309 $[M - H]^-$), which was indicative of eight degrees of unsaturation. The UV spectrum of **29** showed the absorption maxima at 204, 226, and 279 nm. The 1D- and 2D NMR data (Table 3) of **29** resembled those of **25**, and one of the major differences was the replacement of a methyl group at C-2 in **25** by an isopropyl motif (δ_C 26.1, C-7; δ_C 22.6, C-8/C-9) at the same position in **29**, as supported by the HMBC correlations from H_3-8/H_3-9 (δ_H 1.11) to C-2 and from H-3 (δ_H 6.84) to C-7 as well as a COSY correlation of H-7 (δ_H 3.11) to H_3-8/H_3-9. The other major difference was the replacement of an isopropyl motif at C-5 in **29** by a methyl group (δ_C 18.9, C-10) at the same position in **29**, which was confirmed by the HMBC correlations from H_3-10 (δ_H 2.02) to C-4 and C-6. The planar

structure of **29** was further confirmed with the aid of 2D NMR spectroscopic analysis (Fig. 3). Thus, compound **29** was assigned to be 4-*C*-*p*-hydroxybenzylthymol, which was renamed capillarisenol D.

The molecular formula of compound **31** was determined to be $C_{25}H_{22}O_9$ by its HR-ESI-TOF-MS at *m*/*z* 465.1051 [M - H]$^-$. The UV absorption at 215 and 267 nm implied the existence of an aromatic ring in **31**. The ^{13}C NMR spectrum of **31** revealed that this compound contained 25 carbons, which consisted of two methylene, one methine, two olefinic, eighteen aromatic, and two carbonyl carbons. In the ^{1}H NMR spectrum, two double doublets at δ_H 2.87 (dd, J = 8.7, 14.4 Hz) and 2.98 (dd, J = 3.4, 14.4 Hz) were attributed to the geminal protons of the benzylic methylene, which were coupled with a double doublet at δ_H 4.98 (dd, J = 3.4, 8.7 Hz), assignable to the oxymethine proton. The characteristic ABX-type aromatic proton signals at δ_H 6.49 (dd, J = 1.1, 8.1 Hz), 6.62 (d, J = 8.1 Hz), and 6.67 (d, J = 1.1 Hz) suggested the presence of a 1,3,4-trisubstituted aromatic ring. These data indicated that compound **31** had a similar structure to rosmarinic acid (compound **17**) (Petersen and Simmonds, 2003). In comparison with the ^{1}H NMR spectrum of rosmarinic acid, two doublets at δ_H 6.11 and 7.81 (J = 15.7 Hz) and two singlets at δ_H 6.60 and 7.10 were observed in the spectrum of **31** instead of the characteristic ABX-type aromatic proton signals in that of rosmarinic acid. Based on this finding, a 1,2,4,5-tetrasubstituted aromatic ring of *trans*-caffeoyl moiety was present in the molecule of **31** in place of the 1,3,4-trisubstituted one of rosmarinic acid, which was also supported by λ^{max} at 288 and 340 nm in the UV spectrum as well as by ^{13}C NMR data (Table 2). In addition, a pair *ortho*-coupling protons were observed at δ_H 6.65 and 6.87, accompanied by diphenyl methylene protons at δ_H 3.81. Therefore, it was suggested that a 4-hydroxybenzylic moiety was attached to C-6 of rosmarinic acid, which was further supported by the presence of signals at δ_C 36.4, 115.2 (2C), 129.2 (2C), 131.1, and 155.4 in ^{13}C NMR spectrum and by the HMBC correlations of H-7'' to C-1/C-5 and H-5 to C-7'' (Fig. 2). Compound **31** showed a specific rotation of + 76.7° (in methanol), which was the same behaviour as that of rosmarinic acid ($[\alpha]_D^{25}$: + 70.8°). Therefore, it was proposed that the stereochemistry at C-8′ was *R* configuration. Thus, compound **31** was deduced to be 6-*C*-*p*-hydroxybenzylrosmarinic acid, which was renamed capillarisenol E.

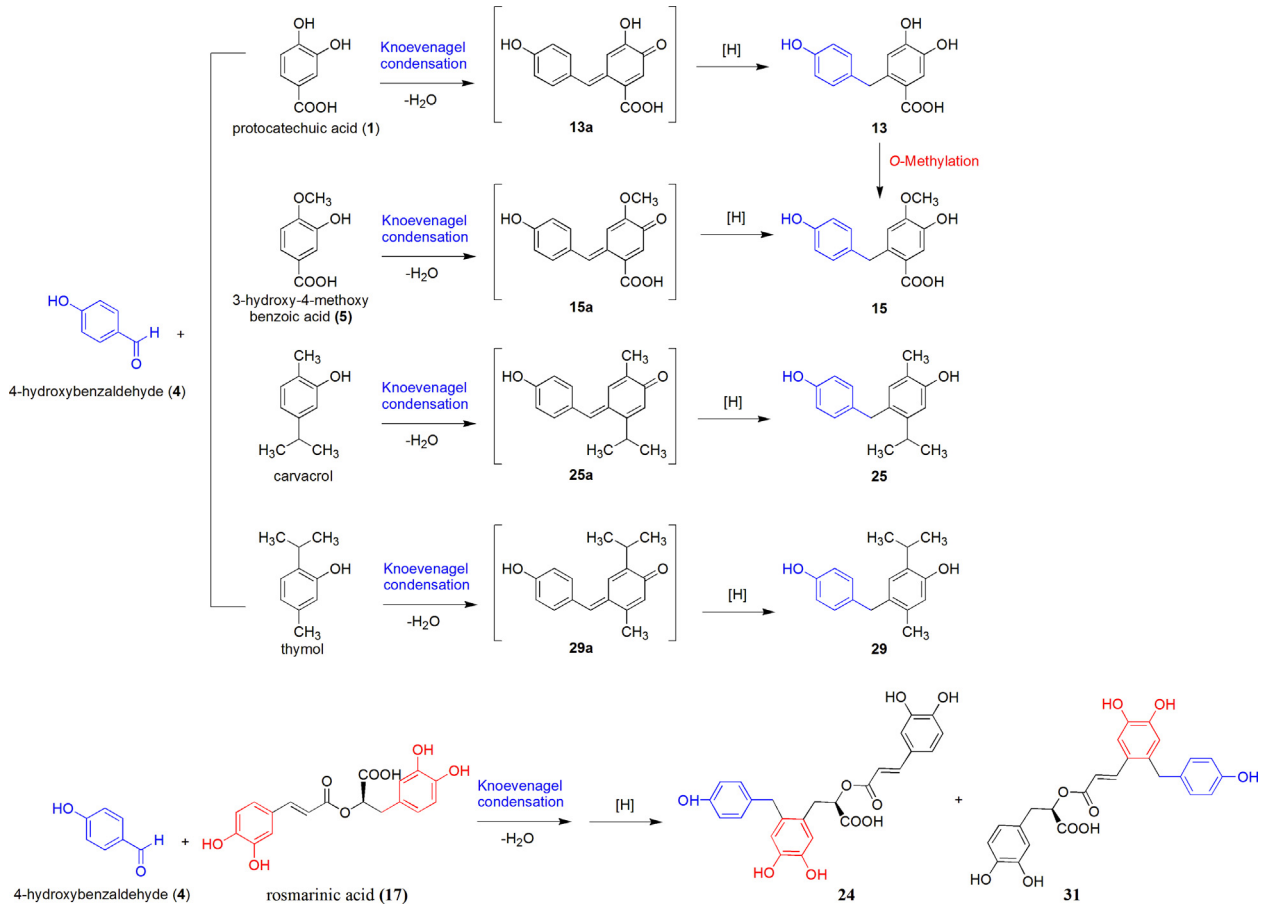
3.2. Structural elucidation of another new aromatic compound 32

Compound **32** was obtained as yellow oil, with the molecular formula $C_{19}H_{22}O_7$ based on its HR-ESI-TOF-MS at *m*/*z* 385.1203 [M + Na]$^+$. The UV absorption at 215 and 267 nm of **32** indicated the presence of an aromatic ring. The ^{1}H NMR spectrum of **32** exhibited six aromatic [δ_H 7.20 (2H, s, H-2 and H-6), 7.37 (2H, d, J = 8.5 Hz, H-2′ and H-6′), 6.92 (2H, d, J = 8.5 Hz, H-3′ and H-5′)], one methine [δ_H 4.88 (1H, m, H-7′)], one methylene [δ_H 4.25 (2H, m, H-8′)], and four methoxyl [δ_H 3.81 (6H, s, H_3-8 and H_3-10), 3.74 (3H, s, H_3-9′), 3.73 (3H, s, H_3-9)] proton signals. The ^{13}C NMR and DEPT-135 spectra showed 19 carbon resonances shared by twelve aromatic, four methoxyl, one carbonyl, one methine, and one methylene carbons. The ^{1}H- and ^{13}C NMR spectral data of **32** are listed in Table 4, and the signal assignments were determined by the HSQC technique. The ^{1}H–^{1}H COSY correlations led to the establishment of three spin-coupling systems in **32** (blue bold lines in Fig. 3). Combined with ^{1}H NMR, ^{13}C NMR, and HRESIMS, one hydroxyl group and one carbonyl group were found in compound **32**. The hydroxyl group was attached to C-7′, which was confirmed by the chemical shifts of the methine carbon of C-7′ (69.8) as well as the HMBC correlation of H-2′/C-7′. One carbonyl group was located at C-1, which was confirmed by the HMBC correlation of H-2/C-7. Four methoxyl groups were attached to C-3, C-4, C-5, and C-4′ based on the HMBC correlations of H-8/C-3, H-9/C-4, H-10/C-5, and H-9′/C-4′, respectively. To further determine the absolute configuration at C-7′, the molecular optical rotation value of compound **32** were compared with that of *R*-suspensaside and *S*-suspensaside (Guo, et al., 2007). Compound **32** showed a specific rotation of −4.6° (methanol), which was nearly equal to that of *S*-suspensaside ($[\alpha]_D^{25}$ = -4.7°). This method was successfully applied previously for the configuration confirmation (Ge, et al., 2018; Ma, et al., 2016; Xiao, et al., 2022). Therefore, it was proposed that the stereochemistry at C-7′ was *S* configuration. Based on the analysis, the structure of **32** was thus determined to be (7′*S*)-2-hydroxy-2-(4-methoxyphenyl)ethy l3,4,5-trimethoxy benzoate.

The other known compounds were identified as protocatechuic acid (**1**) (Li, et al., 2022), protocatechuyl aldehyde (**2**) (Li, et al., 2005), 4-hydroxybenzoic acid (**3**) (Zhang, et al., 2021), 4-hydroxybenzaldehyde (**4**) (Zhang, et al., 2021), 3-hydroxy-4-methoxybenzoic acid (**5**) (Yang, et al., 2017), 3-hydroxy-4-methoxy-benzaldehyde (**6**) (Yang, et al., 2017), caffeic acid (**7**) (Ge, et al., 2018), 3,5-dimethoxy-4-hydroxybenzoic acid (**8**) (Feng, et al., 2011), cumaric acid (**9**) (Ge, et al., 2018), 3,4,5-trimethoxybenzoic acid (**10**) (Feng, et al., 2011), 3,4-dihydroxybenzoic acid ethyl ester (**11**) (Yin, et al., 2013), 3,4, α-trihydroxy-methyl phenylpropionate (**12**) (Gu, et al., 2007), amburoside A (**14**) (Sauvain, et al., 1999), *trans*-6-[(1*E*)-2-carboxyethenyl]-3-(3,4- dihydroxyphenyl)-2,3-dihydro-1,4-ben zodioxin-2-carboxlic acid (**16**) (Wan, et al., 2008), rosmarinic acid (**17**) (Refaey, et al., 2021), 2-(3-hydroxy-4-methylphenyl) propanoic acid (**18**) (Austgulen, et al., 1987), caffeic acid ethyl ester (**19**) (Ge, et al., 2018), amburoside B (**20**) (Sauvain, et al., 1999), (+)-*epi*-pinoresinol (**21**) (Ge, et al., 2019), (+)-diasyringaresinol (**22**) (Chang, et al., 1998), (+)-lirioresinol A (**23**) (Liu, et al., 2013), 2-caffeoyloxy-3-[2-(4-hydroxyben zyl)-4,5-dihydroxy]phenylpropionic acid (**24**) (Kikuzaki and Nakatani, 1989), isosalvianolic acid C (**26**) (Liu, et al., 2014), *cis*-*p*-hydroxyl ethyl cinnamate (**27**) (Lu, et al., 2015), *trans*-*p*-hydroxyl ethyl cinnamate (**28**) (Lu, et al., 2015), sakuranetin (**30**) (Ferreira, et al., 2020), luteolin (**33**) (Ferreira, et al., 2020), apigenin (**34**) (Ferreira, et al., 2020), 8-*C*-*p*-hydroxybenzylluteolin (**35**) (Merghem, et al., 1995), 3,4,α-Trihydroxy- isobutylphenylpropionate (**36**) (Gu, et al., 2007), isobutyl protocatechuate (**37**) (Li, et al., 2022), and 5,6-dihy droxy-7,3′,4′-trimethoxyflavone (**38**) (Sato and Tamura, 2015).

3.3. Hypothetical biogenetic pathway for new bisphenols

The hypothetical biogenetic pathway for four new bisphenols (**13**, **15**, **25**, **29**) is shown in Scheme 1. The reaction may be derived from the precursor of 4-hydroxybenzaldehyde (**4**), with



Scheme 1 Hypothetical biogenetic pathway for new bisphenols (**13**, **15**, **25**, **29**, **31**).

a subsequent attack on protocatechuic acid (**1**), 3-hydroxy-4-methoxy benzoic acid (**5**), carvacrol, and thymol, respectively, through a Knoevenagel condensation reaction and eduction of the exocyclic double bond, then yielded capillarisenols A-D. Furthermore, 4-hydroxybenzaldehyde (**4**) and rosmarinic acid (**17**) could also follow the same hypothetical biogenetic pathway to generate compounds **24** and **31** (capillarisenol E). This biogenetic pathway plausibly elucidates the structures of new bisphenols.

3.4. Anti-hepatoma activities of all compounds (1–38)

The anti-hepatoma activities of all compounds are shown in Table 5. Of the five new bisphenols (capillarisenols A-E), only capillarisenol C (**25**) exhibited significant inhibition of Huh7 and HepG2 cells proliferation, with IC_{50} values of 4.96 and 8.58 μM, respectively. While the first-line anti-HCC drug lenvatinib exhibited anti-hepatoma activities against Huh7 and HepG2 cells with IC_{50} values of 29.85 and 30.17 μM, respectively. In addition, new compound **32** also showed significant inhibition of Huh7 and HepG2 cells proliferation, with IC_{50} values of 40.27 and 16.56 μM, respectively. Luteolin (**33**) is a common flavonoid, and its IC_{50} values for Huh7 and HepG2 cells inhibition were 38.14 and 21.07 μM. These results indicated that capillarisenol C is a potential anti-cancer compound, and its mechanism is under study.

Table 5 Anti-hepatoma activities (IC_{50}) of thirty-eight compounds (**1**–**38**).

Compounds	Huh7 IC_{50} (μM)	HepG2 IC_{50} (μM)
25	**4.96**	**8.58**
32	**40.27**	**16.56**
33	**38.14**	**21.07**
34	> 50	**41.82**
Lenvatinib	**29.85**	**30.17**

The IC_{50} of other compounds were greater than 50 μM.

4. Conclusion

Yin-Chen, which belongs to the *Asteraceae* family and the genus *Artemisia*, is among the most abundantly used traditional medicines in China for treating hepatitis and bilious disorder. In this study, chemical investigation of aerial parts of *Artemisia capillaris* Thunb. in Ganzhou resulted in the isolation of five novel bisphenols, capillarisenols A–E (**13**, **15**, **25**, **29**, **31**), and one new phenolic compound (**32**), along with 32 eight known phenolic compounds (**1**–**12**, **14**, **16**–**24**, **26**–**28**, **30**, **33**–**38**).

Bisphenol A (BPA; 2,2-bis(4-hydroxyphenol) propane) is a bisphenol that was first developed as a synthetic oestrogen by Dianin in 1891, and its oestrogenic activity was discovered in 1936 (Dodds and Lawson, 1936). Although BPA is recognised as a synthetic oestrogen, it is rapidly becoming one of the most produced and used chemicals

worldwide. Because BPA can be polymerised into polycarbonate plastic due to its light weight, transparency, colouring, impact resistance, heat resistance, chemical resistance, lack of change over time, and easy moulding and thermoforming. BPA can leach out of food or beverage containers and be ingested (Zalko, et al., 2011), causing many human diseases, such as diabetes, obesity, cardiovascular, chronic respiratory, and kidney disease, and breast cancer (Rezg, et al., 2014; Rochester, 2013; Vandenberg, et al., 2012). Therefore, BPA has been banned from use in the food industry, especially in baby food. Currently, there are a series of bisphenol derivatives (e.g., BPB, BPF, BPS) that are potential substitutes for BPA, a widely studied typical endocrine-disrupting chemical, but they have shown little success (Eladak, et al., 2015; Wang, et al., 2021).

Capillarisenols A-E are the first examples of naturally occurring bisphenols in *Artemisia capillaris* Thunb. They were not cytotoxic. Only Capillarisenol C showed significant anti-hepatoma activity in Huh7 and HepG2 cells, with IC_{50} values of 4.96 and 8.58 μM, better than the positive control drug (Lenvatinib). These results provide new ideas for the study of BPA substitutes as well as phytochemical evidence for the further development and utilisation of *A. capillaris* in health products.

5. Notes

The authors declare no competing financial interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.arabjc.2023.104580.

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