Phenolic Constituents from the Stems of *Morus nigra* and their α -Glucosidase Inhibitory Activities

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Pharmaceut Fronts 2021;3:e8–e12.

Abstracts

Keywords

- Moraceae
- *Morus nigra*
- sanggenon-type flavanone
- nigragenon F
- α -glucosidase

A new sanggenon-type flavanone, nigragenon F (1), together with 11 known compounds, *trans*-resveratrol (2), (*E*)-4-isopentenyl-3,5,2',4'-tetrahydroxystilbene (3), notabilisin E (4), notabilisin A (5), morusin (6), petalopurpureanol (7), 8-geranyl-5,7-dihydroxycoumarin (8), 2,4-dihydroxybenzaldehyde (9), 4-ethoxy-2,6-dihydroxybenzoic acid (10), 3-hydroxy-4-methoxybenzaldehyde (11), and 4-hydroxybenzaldehyde (12), were isolated from the stems of *Morus nigra*. Compound 10 was a new natural product, compounds 3, 4, 7, and 8 were reported from the *Morus* genus for the first time. All of the isolated compounds were evaluated for their α -glucosidase inhibition activity. Among them, six compounds showed obvious inhibitory effects against α -glucosidase with IC₅₀ values ranging from 1.24 to 19.00 μ mol/L.

Introduction

As a metabolic chronic disease, diabetes has severely affected people's health. Evidence suggested that α -glucosidase inhibitors, such as acarbose, miglitol as well as voglibose, can lower the glucose levels in plasma by delaying the absorbance of carbohydrates, and are used clinically to treat diabetes; however, they also bring adverse reactions such as abdominal pain, flatulence, and diarrhea.¹ Thus, the discovery of natural, side-effect-free, and effective α -glucosidase inhibitors from widely sourced medicinal plants are of important value for the treatment of diabetes.

Hyperglycemia is the major symptom of diabetes. It is well known that *Morus* plants are famous for their anti-hyperglycemia effects, and has received much attention in diabetes treatment. The isolated alkaloids from *Morus* plants, such as 1-deoxynojirimycin, and phenolic compo-

nents have demonstrated antidiabetes activity by exhibiting potent α -glucosidase inhibitory activity.^{2,3} Thus, *Morus* plants may be a natural source for drug discovery for diabetes therapy.

Morus nigra Linn., as a deciduous shrub or tree, belongs to the *Morus* genus (Moraceae). The plant of *M. nigra* was introduced from western Iran in the 16th century and mainly distributed in southern Xinjiang province, China.⁴ Our previous program for screening antidiabetic bioactive substances has afforded a series of active compounds from *M. nigra*.^{5–7} As a continuous study, this research provided 12 compounds (1–12), including a new sanggenon-type flavanone (1) and a new natural product (10). All of them were evaluated for their α -glucosidase inhibition activity, and six compounds showed significant inhibitory activity with IC₅₀ values ranging from 1.24 to 19.00 μ mol/L. Our article provided novel potential compounds for the treatment of diabetes in the future.

received
February 2, 2021
accepted
April 30, 2021

DOI <https://doi.org/10.1055/s-0041-1730957>
ISSN 2628-5088.

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Materials and Methods

General Methods

Ultraviolet (UV) spectra were collected using a UV-2500 PC instrument (Shimadzu Corporation, Japan). Mass spectrometry was determined on a Waters Xevo G2-XS-Q-TOF. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AV III instrument. Electronic circular dichroism spectra were obtained using a JASCO-810 spectropolarimeter. Silica gel (200–300 mesh, Qingdao Haiyang Chemical Co, Ltd.), Sephadex LH-20 (GE Healthcare, Sweden), and RP-C18 (YMC Co., Ltd., Japan) were used for column chromatography (CC). Thin layer chromatography was performed on silica gel HF254 plates using 10% H₂SO₄ in ethanol (v/v) spray reagents followed by heating. Semipreparative high-performance liquid chromatography (HPLC) was carried out on a LC3050N HPLC using a C18 column (10 × 250 mm, 5 μm, Waters Corporation, United States) and characteristic UV absorption at 210 nm. Reagents were of analytical reagent grade (Sinopharm Chemical Reagent Co., Ltd., Shanghai, China) except for acetonitrile and methanol which were of chromatographic grade.

Plant Materials

The stems of *M. nigra* L. (Moraceae) were collected from Hetian town, in the Xinjiang province of China in September 2016. The plant was identified by Prof. Tong Wu, who comes from China State Institute of Pharmaceutical Industry, China. A voucher specimen (No. 201609001) was deposited in our department.

Extraction and Isolation

The dried and powered stems of *M. nigra* (15 kg) were extracted twice with 90% aqueous EtOH under hot reflux (1.5 hours each time). The concentrated extract was suspended in water and partitioned successively with petroleum ether (PE), dichloromethane (DCM), ethyl acetate (EtOAc), and *n*-butanol. The crude extracts of DCM portion (120 g) and EtOAc portion (80 g) were mixed and then subjected to silica gel CC, eluted with CH₂Cl₂–CH₃OH (80:1 → 1:1) to obtain six fractions (Fr.A–Fr.F). Fr.A (42.5 g) was purified by silica gel CC (PE–acetone, 15:1 → 1:1) to obtain 18 subfractions (Fr.A-1–Fr.A-18). Fr.A-8 (13.3 g) was decolorized with HP-20 macroporous-absorbing resin eluted with EtOH to get a fraction (Fr.A-8-1). Fr.A-8-1 was further separated by CC successively over Sephadex LH-20 (CH₂Cl₂–CH₃OH, 1:1) and RP-C18 (CH₃OH–H₂O, 50:50 → 100:0) to obtain five fractions (Fr.A-8-1-a–Fr.A-8-1-e). Fr.A-8-1-a (56.0 mg) was purified by semipreparative HPLC (CH₃CN–H₂O, 18:82) to yield compound **9** (1.7 mg) and compound **11** (3.5 mg). Fr.A-8-1-b (14.7 mg) was separated by semipreparative HPLC eluted with a gradient of CH₃CN–H₂O (28:72 → 35:65) to afford compound **10** (3.0 mg). Fr.A-9 (1.3 g) was chromatographed over Sephadex LH-20 (CH₂Cl₂–CH₃OH, 1:1), followed by CC on RP-C18 (CH₃OH–H₂O, 60:40 → 90:10), to give two fractions (Fr.A-9-1–Fr.A-9-2). Fr.A-9-2 (30.0 mg) was further subjected to semipreparative HPLC (CH₃CN–H₂O, 25:75) to yield compound **12** (3.0 mg). Fr.A-11 (0.8 g) was chromatographed on Sephadex LH-20 (CH₂Cl₂–CH₃OH, 1:1) to give a fraction (Fr.A-11-3). Fr.A-11-3

(125.7 mg) was separated by silica gel CC (CH₂Cl₂–CH₃OH, 100:1 → 10:1) to obtain two fractions (Fr.A-11-3-1–Fr.A-11-3-2). Fr.A-11-3-1 (18.5 mg) and Fr.A-11-3-2 (35.4 mg) were further purified by semipreparative HPLC to yield compound **6** (2.0 mg) and compound **7** (11.4 mg), respectively. Fr.A-13 (3.4 g) was chromatographed over Sephadex LH-20 (CH₂Cl₂–CH₃OH, 1:1) to produce a fraction (Fr.A-13-1), which was subjected to CC on RP-C18 (CH₃OH–H₂O, 50% → 100%) to produce three parts (Fr.A-13-1-1–Fr.A-13-1-3). Fr.A-13-1-1 (174.5 mg) and Fr.A-13-1-2 (82.7 mg) were further purified by semipreparative HPLC (CH₃CN–H₂O, 70:30) to afford compounds **1** (5.6 mg) and **4** (3.6 mg), respectively. By a similar procedure to Fr.A-13, Fr.A-14 (1.4 g) was subjected successively to CC on Sephadex LH-20 (CH₂Cl₂–CH₃OH, 1:1) and RP-C18 (CH₃OH–H₂O, 50:50 → 90:10), followed by semipreparative HPLC, to yield compound **5** (26.6 mg). Fr.B (6.6 g) was initially isolated by Sephadex LH-20 (CH₂Cl₂–CH₃OH, 1:1), followed by RP-C18 eluted with CH₃CN–H₂O (20:80 → 70:30) to yield six fractions (Fr.B-1–Fr.B-6). Fr.B-2 (107.3 mg) was chromatographed on silica gel CC (CH₂Cl₂–CH₃OH, 60:1, 50:1, 40:1, 20:1, 10:1) to give one fraction (Fr.B-2-1), which afforded compound **8** (1.0 mg) by semipreparative HPLC (CH₃CN–H₂O, 48:52). Fr.D (15.0 g) was initially divided into three fractions (Fr.D-1–Fr.D-3) by CC on silica gel (PE–acetone, 5:1, 3:1, 2:1, 1:1). Fr.D-2 (5.0 g) was separated by Sephadex LH-20 (CH₂Cl₂–CH₃OH, 1:1) to give four subfractions (Fr.D-2-1–Fr.D-2-4). Fr.D-2-2 (1.0 g) was isolated into three portions (Fr.D-2-2-1–Fr.D-2-2-3) by CC on RP-C18 (CH₃OH–H₂O, 10:90 → 90:10). Fr.D-2-2-1 (47.7 mg) was further purified by semipreparative HPLC (CH₃CN–H₂O, 23:77) to yield compound **2** (3.3 mg). Fr.D-3 (4.1 g) was subjected to CC on Sephadex LH-20 twice, eluted with CH₂Cl₂–CH₃OH (1:1) to get one portion (Fr.D-3-2), which was further separated by CC on RP-C18 (CH₃OH–H₂O, 10:90 → 90:10) to afford four fractions (Fr.D-3-2-a–Fr.D-3-2-d). Fr.D-3-2-d (10.2 mg) was purified by semipreparative HPLC to obtain compound **3** (2.0 mg).

α-Glucosidase Inhibition Assay

The α-glucosidase inhibitory activity was assessed with a spectrophotometric method⁸ using acarbose as the positive control. Sample solution with six different concentrations was preincubated with α-glucosidase (0.2 U/mL, Sigma Chemical Co. St. Louis, Missouri, United States) in 96-well plates at 37°C for 10 minutes. Then the substrate 4-nitrophenyl-α-D-glucosidase (PNPG, 100 μL, 2 mmol/L, Sigma Chemical Co., United States) was added to each well. After incubation at 37°C for 20 minutes, the reaction was terminated with Na₂CO₃ solution (50 μL, 1.06 g/50 mL). The absorbance of the system was measured at 405 nm using a microplate reader. The IC₅₀ was performed in triplicate and calculated with Graphpad Prism 7.0.

Results and Discussion

Structure Identification

Compound **1** was obtained as yellow powder. The molecular formula was established as C₂₅H₂₆O₈ according

Table 1 ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) data of **1** (in acetone- d_6)

Position	δ_{H} (J in Hz)	δ_{C}
2		92.2
3	7.07 br s (OH)	102.5
4		188.4
4a		100.8
5	11.77 s (OH)	164.4
6	5.80 s	90.7
7		171.6
8		106.9
8a		159.5
9a	3.13 dd (14.8, 9.2)	32.1
9b	2.82 dd (14.8, 6.0)	
10	5.24 br t (7.6)	119.0
11		136.6
12	1.51 s	25.9
13	1.61 s	18.1
14	3.04 d (8.4)	26.5
15	4.77 br t (8.4)	93.2
16		71.5
17	1.23 s	25.9
18	1.22 s	25.2
1'		121.3
2'		161.3
3'	6.39 d (2.0)	99.5
4'	8.72 br s (OH)	161.3
5'	6.52 dd (8.4, 2.0)	109.8
6'	7.36 d (8.4)	125.8

to the $[\text{M} - \text{H}]^-$ ion peak at m/z 453.1555 (calcd. for $\text{C}_{25}\text{H}_{25}\text{O}_8$, 453.1549) in its HRESIMS (high-resolution electrospray ionization mass spectrometry) spectrum. UV absorption maxima of compound **1** were recorded at 235 (sh), 285 (sh), and 310 nm, indicating the presence of a sanggenon-type flavanone framework (3-hydroxy-2-prenylflavanones with a furan moiety between the B and C rings) in this compound.⁹ Besides, IR spectrum of compound **1** showed the existence of OH ($3,395\text{ cm}^{-1}$), C=O ($1,657\text{ cm}^{-1}$), and benzene ring ($1,608$ and $1,463\text{ cm}^{-1}$). Furthermore, the ^1H NMR spectrum of compound **1** (►Table 1) showed (1) the signals of a hydrogen-bonded hydroxy group at δ_{H} 11.77 (1H, br s, OH-5); (2) an aromatic ABX spin system at δ_{H} 7.36 (1H, d, $J=8.4\text{ Hz}$, H-6'), 6.52 (1H, dd, $J=8.4, 2.0\text{ Hz}$, H-5'), and 6.39 (1H, d, $J=2.0\text{ Hz}$, H-3'); (3) an aromatic proton at δ_{H} 5.80 (1H, s, H-6); and (4) a characteristic isoprenyl of sanggenon-type flavanone at δ_{H} 5.24 (1H, br t, $J=7.6\text{ Hz}$, H-10), 3.13 (1H, br dd, $J=14.8, 9.2\text{ Hz}$, H-9a), 2.82 (1H, br dd, $J=14.8, 6.0\text{ Hz}$, H-9b), 1.61 (3H, br s, H-13), and 1.51 (3H, br s, H-12).⁷ In addition, signals of another cyclized isoprenyl

group were observed at δ_{H} 4.77 (1H, br t, $J=8.4\text{ Hz}$, H-15), 3.04 (2H, br d, $J=8.4\text{ Hz}$, H-14), 1.23 (3H, s, H-17), and 1.22 (3H, s, H-18). A total of 25 carbon signals appeared in the ^{13}C -NMR spectrum (►Table 1), including 20 carbon signals from the sanggenon skeleton and 5 carbon signals from the substituent. The key HMBC correlations of H₂-9 to C-3 and C-1' assigned the isoprenyl group at C-2, confirming the sanggenon skeleton of **1**. The HMBC correlations from H₂-14 to C-8a and C-16, and from H-15 to C-7, C-17, and C-18 indicated that the cyclized isoprenyl group was fused at C-7 and C-8. Thus, its planar structure was established as shown in ►Fig. 1. Furthermore, the absolute configurations of C-2 and C-3 in **1** were assigned as 2R and 3S respectively, according to the positive Cotton effects at 219, 251, 296, and 317 nm, and negative Cotton effects at 239 and 276 nm in its circular dichroism (CD) spectrum¹⁰ (see ►Supplementary Figs. S1, S2, S3, S4, S5, S6 [online only]). The absolute configuration of C-15 remained to be determined. Therefore, compound **1** was elucidated as (6aS,11bR)-6a,11b-dihydro-5,6a,9-trihydroxy-2-(1-hydroxy-1-methylethyl)-11b-(3-methyl-2-buten-1-yl)-1H,2H,6H-benzofuro[3,2-b]pyrano [2,3-e]-[1]benzofuro-6-one, and was named nigragenon F.

The structures of the remaining 11 compounds (Fig. 1) were elucidated as *trans*-resveratrol (**2**),¹¹ (*E*)-4-isopentenyl-3,5,2',4'-tetrahydroxystilbene (**3**),¹² notabilisin E (**4**),¹³ notabilisin A (**5**),¹¹ morusin (**6**),¹⁴ petalopurpureanol (**7**),¹⁵ 8-geranyl-5,7-dihydroxycoumarin (**8**),¹⁶ 2,4-dihydroxybenzaldehyde (**9**),¹⁷ 4-ethoxy-2,6-dihydroxybenzoic acid (**10**),¹⁸ 3-hydroxy-4-methoxybenzaldehyde (**11**),¹⁹ and 4-hydroxybenzaldehyde (**12**)²⁰ by comparing their ^1H and ^{13}C NMR spectral data with those reported in the literature. Compound **10** was a new natural product, and **3**, **4**, **7**, and **8** were reported from the *Morus* genus for the first time.

Compound **1**, nigragenon F, yellow powder; $[\alpha]_{\text{D}}^{25} +66.9$ (c 0.23, MeOH); UV λ_{max} (MeOH) (log ϵ) 210 (3.03), 235 (sh) (1.32), 285 (sh) (3.09), 310 (4.94) nm. CD (MeOH) λ_{max} ($\Delta\epsilon$) 219 (+2.31), 239 (−0.03), 251 (+0.57), 276 (−0.38), 296 (+0.72), 317 (+0.75) nm; IR (KBr) ν_{max} 3395, 2925, 1657, 1622, 1608, 1463, 1378, 1149 cm^{-1} ; ^1H and ^{13}C NMR data, see ►Table 1. Negative ion HRESIMS m/z : 453.1555 $[\text{M} - \text{H}]^-$ (calcd. for $\text{C}_{25}\text{H}_{25}\text{O}_8$, 453.1549).

Compound **10**, 4-ethoxy-2,6-dihydroxybenzoic acid, yellow-brown powder; MS (ESI) m/z : 197.04 $[\text{M} - \text{H}]$, molecular formula: $\text{C}_9\text{H}_{10}\text{O}_5$; ^1H -NMR (400 MHz, CD_3COCD_3); δ_{H} 10.01 (2H, br s, OH-2/6), 5.93 (2H, s, H-3/5), 4.56 (2H, q, $J=7.2, 7.2\text{ Hz}$, H-7), 1.44 (3H, t, $J=7.2\text{ Hz}$, H-8); ^{13}C -NMR (100 MHz, CD_3COCD_3); δ_{C} 169.9 (C-9), 164.8 (C-4), 163.0 (C-2/6), 95.5 (C-3/5), 93.3 (C-1), 62.1 (C-7), 13.7 (C-8).

α -Glucosidase Activity Screening

Compounds **1**–**12** were evaluated for their α -glucosidase inhibitory activity. All of them were initially tested for their inhibitory rates at the concentration of 100 $\mu\text{mol/L}$. Preliminary result showed that compounds **3**–**8** exhibited obvious inhibitory effect with inhibition rates of more than 90%, while the rest of the compounds with inhibition rates of below 50%. Then, IC_{50} values of **3**–**8** were further determined. They showed potent inhibitory activities with IC_{50} values

Fig. 1 Structures of compounds 1-12 isolated from *M. nigra*.

Table 2 The α -glucosidase inhibitory activities

Compounds	IC ₅₀ (μ mol/L) ^a
1	–
2	–
3	19.00 (17.49–20.45)
4	1.72 (1.43–2.09)
5	1.24 (1.19–1.27)
6	4.72 (4.01–5.91)
7	4.38 (2.35–5.80)
8	12.01 (11.88–13.40)
9	–
10	–
11	–
12	–
Acarbose ^b	987.90 (874.70–1041.20)

^aIC₅₀ was afforded with confidence interval ($n = 3$) and adopted 95% confidence interval; “–”: IC₅₀ > 100 μ mol/L.

^bPositive control.

ranging from 1.24 to 19.00 μ mol/L (**Table 2**). Of these, compound **5** showed the highest α -glucosidase inhibitory effect with IC₅₀ value of 1.24 μ mol/L, approximately 800 times stronger than the positive control drug acarbose.

Conclusion

In the present study, phytochemistry investigation on the stems of *M. nigra* afforded 12 compounds (**1–12**), including a new sanggenon-type flavanone, a new natural product, and four compounds firstly reported from the *Morus* genus. The α -glucosidase inhibitory effect test provided different struc-

ture-type α -glucosidase inhibitors from *M. nigra*, not only enriching the library of natural α -glucosidase inhibitors, but also laying experimental basis for the development and utilization of *M. nigra* as hypoglycemic medicinal plant resources.

Funding

This work was supported by the Natural Science Foundation of Shanghai (Grant No.19ZR1454400), the National Natural Science Foundation of China (Grant No. 81803844), and the National Science and Technology Major Project (Grant No. 2018ZX09731-016).

Conflict of Interest

The authors declare no conflict of interest.

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