The Chemical Constituents of Diaphragma Juglandis Fructus and Their Inhibitory Effect on α-Glucosidase Activity

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Abstract: In our current investigation, 37 constituents (1–37), including 11 megastigmanes (1–11), 17 flavonoids (12–28) and 9 phenylpropanoids (29–37), were isolated from a 70%-EtOH extract of Diaphragma juglandis Fructus. Among them, compounds 1–3, 12 and 29 were new compounds and their structures were elucidated on the basis of physicochemical evidence and meticulous spectroscopic analysis (NMR, HRESIMS and CD). Compounds 13, 16, 21 and 28 showed moderate inhibitory effect on α-glycosidase inhibitory activities, with IC50 values being in the range of 29.47–54.82 µM and stronger than the positive control (acarbose, 60.01 ± 4.82 µM).

Keywords: walnut; megastigmanes; bicyclic neomegastigmane; flavonoids; phenylpropanoids; α-glucosidase inhibition activity

1. Introduction

The walnut (Juglans regia L.) is consumed globally as a high economic value crop [1]. The edible portion of walnuts (kernel) has been processed into many types of foods due to its unique and highly nutritious nature and health-related benefits [2]. However, Diaphragma juglandis Fructus, the dry wooden diaphragm inside the walnut, mainly consists of undigestible fiber and lignin and is usually discarded as waste during the processing of the walnut [3]. In fact, Diaphragma juglandis Fructus is a traditional Chinese medicine and has been used to treat several illnesses such as insomnia, diarrhea, kidney deficiency and reproductive diseases for a long time [4,5]. It has also been used as an herbal tea and a dietary supplement in folk culture [6]. The research shows that Diaphragma juglandis Fructus is rich in a variety of bioactive components, such as flavonoids, saponins, phenolic acids and polysaccharides [7].

Previously, our team focused on the anti-diabetic effect of Diaphragma juglandis Fructus, and it was found to improve symptoms of diabetes via the AKT/FoxO1 signaling pathway [8]. As part of our continuous program to identify new potential candidates to control diabetes using natural products, the subsequent phytochemical study led to the isolation of 37 constituents (1–37) from Diaphragma juglandis Fructus, including 11 megastigmanes (1–11) (Figure 1), (12–28) and 9 phenylpropanoids (29–37). Among them, compounds 1–3, 12 and 29 were new compounds. Their structures were elucidated on the basis of physicochemical evidence, in-depth NMR spectroscopic analysis and high-resolution mass spectrometry. Meanwhile, the α-glucosidase inhibition activities of all isolates were evaluated. The isolation, structural identification and bioactivity evaluation of the obtained compounds are reported herein.
Figure 1. The structures of megastigmanes (1–11) isolated from Diaphragma juglandis Fructus.

2. Results and Discussion

2.1. Structural Elucidation

Compound 1 displayed a quasi-molecular ion peak at \( m/z \) 225.1489 ([M+H]\(^+\), calcld 225.1490), in agreement with the molecular formula C\(_{13}\)H\(_{20}\)O\(_{3}\), corresponding to four degrees of unsaturation. The analysis of \(^1\)H-NMR data (Table 1) revealed that 1 possessed three methyls \([\delta_H 1.00, 1.03, 1.05 (3H each, both s, H\(_3\)-3-10, 11, 12)]\), three methylenes and a methine bearing an oxygen function \([\delta_H 4.08 (1H, d, J = 1.4 \text{ Hz}, H-13)]\). In addition, the \(^{13}\)C-NMR (Figure S4) and DEPT spectra revealed a quaternary carbon bearing an oxygen function \([\delta_C 76.8]\), a trisubstituted olefin \([\delta_H 6.15 (1H, br s, H-4), \delta_C 121.0 (C-4), 168.2 (C-5)]\) and a conjugated carbonyl carbon \([\delta_C 202.6]\). The planar structure of 1 was determined to be a bicyclic neomegastigmane skeleton through the interpretation of various NMR experiments \([9]\), including HSQC, \(^1\)H-\(^1\)H COSY and HMBC spectra. Namely, the \(^1\)H-\(^1\)H COSY experiments of 1 indicated the presence of one partial written in red bold lines (Figure 2). In addition, obvious long-range correlations were observed between the following proton and carbon pairs in the HMBC experiments: \( \text{H}_2-2 \) and \( \text{C}-1, 3, 6; \text{H}-4 \) and \( \text{C}-5, 6, 13; \text{H}-6 \) and \( \text{C}-5; \text{H}_2-8 \) and \( \text{C}-6, 9, 13; \text{H}-13 \) and \( \text{C}-4, 5, 9, 10; \text{H}_3-10 \) and \( \text{C}-8, 9, 13; \text{H}_3-11 \) and \( \text{C}-1, 2, 6, 12; \text{H}_3-12; \) and \( \text{C}-1, 2, 6, 11 \) (blue arrow in Figure 2). Next, the relative stereostructure of 1 was clarified to be 9\(\beta\)-OH and 13\(\beta\)-OH by the NOESY experiment, in which correlations were observed between the following proton pairs: \( \text{H}_2-12 \) and \( \text{H}-6; \text{H}-6 \) and \( \text{H}-13; \text{H}-13; \) and \( \text{H}_3-10 \) (Figure 3). Based on the above-mentioned evidence, the structure of 1 was elucidated to be a bicyclic megastigmane named diamegastigmane A, as shown in Figure 1. Bicyclic megastigmanes are a small but growing group of natural products, and a possible biosynthetic pathway for 1 is further proposed in this paper (Figure 4).

Figure 2. \(^1\)H-\(^1\)H COSY and key HMBC correlations of compounds 1–3.
Figure 3. Key NOESY correlations of compound 1.

Figure 4. Plausible biogenetic pathway for compound 1.

Table 1. $^1$H-NMR (600 MHz, methanol-$d_4$) and $^{13}$C-NMR (150 MHz, methanol-$d_4$) of compounds 1–3 ($\delta$ in ppm, $J$ values in Hz).

| Position | 1   | 2   | 3   |
|----------|-----|-----|-----|
|          | $\delta_H$ | $\delta_C$ | $\delta_H$ | $\delta_C$ | $\delta_H$ | $\delta_C$ |
| 1        | -   | 35.5 | -   | 43.1 | -   | 37.2 |
| 2        | 2.33 (d, 15.6) | 2.61 (d, 18.3) | 50.8 | 1.87 (d, 17.3) | 48.1 |
| 3        | 2.13 (d, 15.6) | 2.20 (d, 18.3) | 200.9 | - | 202.3 |
| 4        | 6.15 (br. s) | 121.0 | 6.10 (br. s) | 122.4 | 5.70 (br. s) | 125.3 |
| 5        | - | 168.2 | - | 173.9 | - | 169.9 |
| 6        | 2.16 (dd, 12.9, 4.5) | 49.2 | - | 78.8 | 1.81 (t, 5.2) | 52.2 |
| 7        | 1.94 (m) | 25.3 | 1.98 (m) | 35.8 | 1.92 (m) | 26.8 |
| 8        | 1.39 (dd, 13.4, 4.0) | 39.1 | 1.67 (m) | 34.9 | 2.19 (m) | 37.6 |
| 9        | 1.86 (ddd, 13.4, 3.7, 3.0) | 1.72 (td, 13.4, 4.3) | 76.8 | 3.67 (m) | 68.9 | 3.73 (m) | 76.5 |
| 10       | 1.03 (s) | 19.3 | 1.16 (d, 6.2) | 23.5 | 1.17 (d, 6.2) | 20.4 |
| 11       | 1.00 (s) | 25.8 | 1.09 (s) | 24.4 | 0.90 (s) | 28.9 |
| 12       | 1.05 (s) | 28.7 | 1.04 (s) | 23.5 | 0.96 (s) | 27.4 |
| 13       | 4.08 (d, 1.4) | 80.2 | 4.39 (t, 1.9) | 63.1 | 1.90 (d, 1.1) | 24.8 |
| 1′       | 4.34 (d, 7.7) | 102.8 |
| 2′       | 3.17 (m) | 75.2 |
| 3′       | 3.39 (m) | 78.0 |
| 4′       | 3.39 (m) | 72.0 |
| 5′       | 3.58 (m) | 75.2 |
| 6′       | 4.56 (dd, 11.8, 2.3) | 64.9 |
| 7′       | 4.42 (dd, 11.8, 6.4) | |
| 1‰       | - | |
| 2‰, 6‰  | 7.89 (d, 8.8) | 132.9 |
| 3‰, 5‰  | 6.83 (d, 8.8) | 116.2 |
| 4‰      | - | 163.7 |
| 7‰      | - | 167.9 |

“m” means multiplet or overlapped with other signals.
Compound 2 was assigned a molecular formula of C_{13}H_{22}O_{4} through an analysis of the HRESIMS ion peak at m/z 485.3115 ([2M+H]^+), calcd 485.3114). The 1H-NMR (Table 1) spectrum showed the presence of two methylene singlets [δ_H 1.04, 1.09 (3H each, both s, H_{3-11}, 12)], a doublet methyl singlet [δ_H 1.16 (3H, d, J = 6.2 Hz, H_{3-10})], a methine and methylene bearing a hydroxyl group [δ_H 3.67 (1H, m, H-9)], 4.39 (2H, t, J = 1.9 Hz, H_{2-13})] and a trisubstituted olefin [δ_H 6.10 (1H, br. s, H-4)]. The 13C-NMR spectrum exhibited 13 carbon signals. In combination with the HSQC spectrum, carbon signals were identified as three methyls [δ_C 23.5 (C-10), 24.4 (C-11), 23.5 (C-12)], four methylenes [δ_C 50.8 (C-2), 35.8 (C-7), 34.9 (C-8), 63.1 (C-13)], an oxygenated methine carbon [δ_C 68.9 (C-9)], a quaternary carbon [δ_C 43.1 (C-1)], an oxygenated quaternary carbon [δ_C 78.8 (C-6)], two olefinic carbons [δ_C 122.4 (C-4), 173.9 (C-5)] and a carbonyl carbon [δ_C 200.9 (C-3)]. The NMR spectroscopic data (Table 1) for 2 closely resembled those of apocynol B, and further analysis of the 2D NMR spectra revealed that the significant difference was the absence of one olefin in the side chain [10]. The 1H-1H COSY spectrum of 2 enabled the identification of the H_{2-7}/H_{2-8}/H_{9}/H_{3-10} unit. Further, HMBC correlations from H_{2-7} to C-1, C-5 and C-6 arranged the carbon chain that connected to C-6 (Figure 2). Moreover, the CD spectrum indicated a 6S-configuration due to a positive Cotton effect at 323 nm and a negative Cotton effect at 272 nm [11]. However, the chirality of C-9 in the side chain was difficult to assign due to the lack of direct evidence and thus, needs to be further determined. Consequently, the structure of 2 was identified (Figure 1) and named diamegastigmane B.

Compound 3 has a molecular formula of C_{26}H_{36}O_{9} based on the HRESIMS ion at m/z 493.2442 ([M+H]^+), calcd 493.2437). The 1H-NMR spectrum (Table 1) of 3 showed two doublet signals at δ_H 7.89 (2H, d, J = 8.8 Hz, H-2",6") and 6.83 (2H, d, J = 8.8 Hz, H-3",5") attributed to the AA'BB' system in a 1,4-substituted benzene ring, assigned to the 4-hydroxybenzoyl group. The location of the 4-hydroxybenzoyl group was established at C-6' in the pyranosyl moiety according to the long-range correlation from a proton signal at δ_H 4.34 (1H, d, J = 7.7 Hz, H-1') to a carbon signal at δ_C 167.9 (C-7") in the HMBC spectrum (Figure 2).

The 1D NMR spectroscopic data (Table 1) of 3 showed significant similarity to those of hirtionoside C, except for the replacement of the gallic acid at the 6'-position by a 4-hydroxybenzoic acid [12]. The absolute configuration at the 6'-position was confirmed to be R by the CD spectrum (positive Cotton effect at 333 nm) [13], and those at the 9-position were also determined to be R by comparing 13C NMR data according to the β-D-glycosylation-induced shift-trend rule [14]. Therefore, the structure of 3 was determined (Figure 1) and named diamegastigmane C.

Compound 12 was obtained as yellow amorphous powder (Figure 5). Its molecular formula was deduced as C_{13}H_{14}O_{6} on the basis of a quasi-molecular ion peak in HRESIMS (C_{14}H_{15}O_{5}, m/z 327.0715 [M+H]^+, calcd 327.0716). The 1H-NMR spectrum of 12 (Table 2) displayed two meta-coupled aromatic protons at δ_H 6.20 (1H, d, J = 2.1 Hz, H-6) and 6.31 (1H, d, J = 2.1 Hz, H-8), together with a singlet at δ_H 8.09 (1H, s, H-2) in the low field. The 13C-NMR spectrum (Table 2) showed 14 carbon signals, including 9 aromatic carbon signals and 5 sugar carbon signals. The 1D NMR spectra data of 12 showed a similar pattern to those of 3,5,7-trihydroxychromone-3-O-α-L-arabinopyranoside, except for the sugar part [15]. The anomeric carbon of 12 at δ_C 109.5 (C-1') and other four sugar carbon signals at δ_C 83.3 (C-2'), 78.7 (C-3'), 87.2 (C-4') and 62.9 (C-5') were similar to those of α-L-arabinofuranose in juglalin [16]. In addition, the structure of the sugar part in 12 was further confirmed to be L-arabinofuranose after derivatization and comparison with an authentic sample in a GC analysis. Based on the above evidence and the 2D NMR spectra (Figure 6), the structure of 12 was elucidated to be 3,5,7-trihydroxychromone-3-O-α-L-arabinofuranoside.
Table 2. $^1$H-NMR (600 MHz, methanol-$d_4$) and $^{13}$C-NMR (150 MHz, methanol-$d_4$) of compound 12. ($\delta$ in ppm, $J$ values in Hz).

| Position | $\delta$H  | $\delta$C | Position | $\delta$H  | $\delta$C |
|----------|------------|-----------|----------|------------|-----------|
| 2        | 8.09 (s)   | 148.7     | 9        | -          | 159.3     |
| 3        | -          | 140.0     | 10       | 1.03 (s)   | 106.4     |
| 4        | -          | 179.0     | 1'       | 5.48 (s)   | 109.5     |
| 5        | -          | 163.4     | 2'       | 4.31 (dd, 3.2, 1.1) | 83.3     |
| 6        | 6.20 (dd, 2.1) | 100.0     | 3'       | 3.94 (dd, 5.9, 3.2) | 78.7     |
| 7        | -          | 166.1     | 4'       | 4.13 (m)   | 87.2      |
| 8        | 6.31 (d, 2.1) | 95.0      | 5'       | 3.78 (dd, 12.1, 3.4) | 62.9     |

"m" means multiplet or overlapped with other signals.

Figure 5. The structures of flavonoids (12-28) isolated from Diaphagma juglandis Fructus. (Ara = $\alpha$-L-arabinofuranose; Xyl = $\beta$-D-xylopyranose; Glc = $\beta$-D-glucopyranose; Gal = $\beta$-D-galactopyranose).

Figure 6. $^1$H-$^1$H COSY and key HMBC correlations of compounds 12 and 29.

Compound 29, a yellow amorphous powder (Figure 7), had a molecular formula of $C_{24}H_{24}O_{10}$ based on HRESIMS at $m/z$ 471.1286 [M-H]$^-$ (calcld for 471.1290) and corresponding to 13 degrees of unsaturation. A comparison of the $^1$H- and $^{13}$C-NMR spectroscopic data of 29 (Table 3) with those of 1,6-di-O-(E)-coumaroyl-$\beta$-D-glucopyranoside (30) suggested that these two compounds were closely related in structure [17], while the variations
mainly occurred in the vicinity of C-7′′ and C-8′′ [C-3′′/5′′ (ΔδC = −1.1), C-4′′ (−1.3), C-9′′ (−2.8), C-2′′/6′′ (+ 2.8) and C-8′′ (+ 0.5)], indicating that 29 was the C-7′′/C-8′′ cis-trans isomerization of 30. The structure of 29 was further confirmed by analysis of coupling constants (J_{C-7}′′ = J_{C-8}′′ = 12.8 Hz in 29 and J_{C-7}′′ = J_{C-8}′′ = 15.9 Hz in 30) and the 2D NMR spectra (Figure 6). Accordingly, the structure of 29 was characterized as 1-O-(Z)-coumaroyl,6-O-(E)-coumaroyl-β-D-glucopyranoside.

Figure 7. The structures of phenylpropanoids (29–37) isolated from Diaphagma juglandis Fructus.

Table 3. 1H-NMR (600 MHz) and 13C-NMR (150 MHz) of 29 in methanol-d_4 (δ in ppm, J values in Hz).

| Position | δH  | δC  | Position | δH  | δC  |
|----------|-----|-----|----------|-----|-----|
| 1        | 5.57 (d, 8.2) | 95.5 | 7′      | 7.64 (d, 15.9) | 146.9 |
| 2        | 3.39 (m) | 73.9 | 8′      | 6.37 (d, 15.9) | 114.9 |
| 3        | 3.48 (m) | 77.9 | 9′      | - | 169.1 |
| 4        | 3.42 (m) | 71.3 | 1′′    | - | 127.4 |
| 5        | 3.67 (m) | 76.3 | 2′′, 6′′ | 7.71 (d, 8.7) | 134.1 |
| 6        | 4.52 (dd, 12.0, 1.9) | 64.4 | 3′, 5′′ | 6.75 (d, 8.7) | 115.9 |
| 1′       | - | 127.2 | 4′     | - | 160.4 |
| 2′, 6′   | 7.45 (d, 8.6) | 131.2 | 7′′    | 6.95 (d, 12.8) | 147.0 |
| 3′, 5′   | 6.79 (d, 8.6) | 116.8 | 8′     | 5.83 (d, 12.8) | 115.4 |
| 4′       | - | 161.3 | 9′     | - | 166.5 |

"m" means multiplet or overlapped with other signals.

In addition, 8 known megastigmanes (blumenol B (4) [18], vomifoliol (5) [19], aglycone of euodionoside G (6) [20], bridelionol C (7) [21], myrsinsonoside A (8) [22], byzantioside B (9) [23], blumenol C glucoside (10) [23] and (6R, 9S)-6′-(4′′-hydroxybenzoyl)-roseoside (11) [24]); 16 known flavonoids, including 5 flavanonols (taxifolin (13) [25] and derivatives [taxifolin-3-β-D-xylopyranoside (14) [26], taxifolin-3-O-α-L-arabinofuranoside (15) [27]], (+)-catechin (16) [28] and derivative [catechin lactone A (17) [29]]), 3 flavanones (naringenin derivatives [naringenin 7-O-β-D-glucopyranoside (18) [30]], eriodictyol derivatives [sakuranetin 5-O-β-D xylopyranoside (19) [30] and (2R)-eriodictyol-5-O-β-D-glucoside
(20) (31)], 7 flavonols (quercetin (21) (32) and derivatives [3-O-methylquercetin (22) (33), aviculin (23) (34), quercetin-3-O-α-D-arabinofuranoside (24) (34), quercetin 3-O-β-D-
xylopyranoside (25) (35), quercetin-3-O-(6′′-O-galloyl)-β-D-galactopyranoside (26) (36) and quercetin-3-O-β-D-glucopyranoside (27) (37)]) and 1 flavone (luteolin (28) (38)); and 8 known phenylpropanoids, including 1 phenylpropionic acid (1,6-di-O-(E)-coumaroyl-β-D-
glucopyranoside (30) (17)), 3 phenylpropanols (erythro-(7S,8R)-guaiacyl-glycerol-β-O-4′-
dihydroconifereryl ether (31) (39), 1-(4′′-hydroxy-3′′-methoxyphenyl)-2-(4′′-(3-hydroxypropyl)-2′′,6′′-dimethoxyphenoxyp)ropane-1,3-diol (32) (40) and rosaleavin B (33) (41)), 1 cyclolignan (5-methoxy-(+)-isolariicresinol (34) (42)), 2 monoepoxylignans (erythro-guaiacyl-glycerol-β-
O-4′-(S′)-methoxylariciresinol (35) (43) and rhoiptelol B (36) (44) and 1 benzofuran lignan (dihydrodehydrodiconiferyl alcohol (37) (45)), were isolated from Diaphagma juglandis Fructus and their structures were determined based on the spectroscopic data and the literature (Figures 1, 5 and 7).

2.2. Glucosidase Inhibitory Assay

Alpha-glucosidase is an enzyme that hydrolyzes the carbohydrates to monosaccharides in the final step of carbohydrate digestion. Therefore, inhibiting the activity of α-glycosidase can effectively inhibit sugar uptake, thereby achieving lowered blood sugar (46). Diaphagma juglandis Fructus was found to improve symptoms of diabetes (8) and the α-glucosidase inhibitory activities (47). In order to search for bioactive substances to treat type 2 diabetes using Diaphagma juglandis Fructus, all isolated constituents (1–37) were assessed for antidiabetic activity using an in vitro α-glycosidase inhibition assay. As shown in Table 4, compounds 13, 16, 21 and 28 exhibited much more potent activity with the IC₅₀ values of 40.39, 54.82, 29.47 and 35.41 µM being lower than the positive control, acarbose (60.01 µM). However, the IC₅₀ values of other compounds were either over the positive control or inactive for α-glycosidase inhibition at 100 µM.

Table 4. α-Glucosidase inhibitory activity of compounds 1–37.

| Compound | IC₅₀ (µM) | Compound | IC₅₀ (µM) |
|----------|----------|----------|----------|
| 1–11     | >100     | 22       | 67.74 ± 6.41 |
| 12       | 92.35 ± 7.24 | 23–25.27 | >100     |
| 13       | 40.39 ± 4.14 | 26       | 77.15 ± 12.36 |
| 14       | 95.78 ± 12.62 | 28       | 35.41 ± 3.87 |
| 15, 17–20 | >100     | 29–34,36,37 | >100     |
| 16       | 54.82 ± 7.47 | 35       | 87.74 ± 13.41 |
| 21       | 29.47 ± 2.95 | Acarbose | 60.01 ± 4.82 |

Data expressed as mean ± SD (n = 3).

Most of the bioactive compounds were flavonoids, suggesting that flavonoids might be the main bioactive substances contributing to the α-glycosidase inhibitory activity of Diaphagma juglandis Fructus. Furthermore, the structures of the A, B and C rings in the flavonoids were closely related to the inhibitory activity. Consistent with the previous reports, comparison among quercetin (21) and luteolin (28) revealed that hydroxylation at the 3-position of flavone enhanced the inhibitory effect. Comparison among (+)-catechin (16), quercetin (21) and luteolin (28) suggested the saturation of the 2,3-double bond in the C ring seemed to decrease the inhibitory activity (48). In addition, among the taxifolin (13) and derivatives (14, 15), taxifolin showed the strongest inhibitory effect, indicating that the presence of a sugar moiety at C-3 may be responsible for the lowered activity (49). In addition, galloyl moieties strengthen the inhibitory effects of flavonoids against the α-glucosidase (such as compound 26) (50).
3. Materials and Methods

3.1. General Experimental Procedures

Optical rotations were determined by a Jasco P-2000 digital polarimeter. CD spectra were recorded on a Bio-Logic MOS-450 spectropolarimeter. One-dimensional (1D) and two-dimensional (2D) NMR spectra were measured on a Bruker 600 spectrometer. HRESIMS data were obtained using a Q Exactive Focus LC-MS/MS spectrometer (Thermo Fisher, MA, USA) or Triple TOF™ 5600 MS/MS system from Applied AB Sciex (Foster City, CA, USA). Medium-pressure liquid chromatography was performed with Buchi C610. To perform the preparative HPLC separation, a C18 preparative HPLC column (21.2 mm × 250 mm, 5 μm, Sharpsil-U C18) on a Shimadzu LC-16P instrument equipped with an RID-20A refractive index detector was used for purification. Silica gel (200–300 mesh, Qingdao Marine Chemical Ltd., Qingdao, China) and RP-18 reversed-phase silica gel (YMC Company Ltd., Tokyo, Japan) were used for column chromatography. All organic solvents were analytical grade (Tianjin zhiyuan Chemical Regents Co., Ltd., Tianjin, China).

The α-glucosidase was obtained from Sigma-Aldrich (Shanghai) Trading Co., Ltd (Shanghai, China). p-nitrophenyl-α-D-glucopyranoside was obtained from Macklin Co., Ltd. (Lot# C12592180, Shanghai, China). Acarbose was purchased from bayer Co., Ltd. (Lot# BJ59027, Beijing, China).

3.2. Plant Material

Diaphragma juglandis Fructus was purchased from Anguo Chinese medicinal materials markets (Hebei Province) in March 2021 and identified by Professor Xiang-ping Pei (Shanxi University of Chinese Medicine). A voucher specimen (No. 20210301) was deposited at Shanxi Modern Chinese Medicine Engineering laboratory (Shanxi University of Chinese Medicine).

3.3. Extraction and Isolation

Diaphragma juglandis Fructus (5 kg) was extracted with 70% EtOH (40 L × 3) and dried under reduced pressure to afford 1.1 kg of crude extract. This extract was then suspended in H2O and partitioned sequentially with petroleum ether (82 g), EtOAc (280 g) and n-butyl alcohol (416 g). The EtOAc partition (260 g) was then fractionated on a silica gel column (CH2Cl2-MeOH, 50:0, 50:1, 30:1, 15:1, 10:1, 5:1, 3:1, 2:1, 1:1, 0:1, v/v) to yield 8 fractions (A-H). Of these, fraction B (15.3 g) was chromatographed on an ODS column (MeOH-H2O, 10–100% MeOH) to yield 15 subfractions (B1-B15). Subfraction B3 was subjected to purification over a preparative HPLC to afford compounds 4 (2.5 mg, tR = 16.5 min) and 5 (3.7 mg, tR = 16.7 min). B4 was further purified by a preparative HPLC to obtain compounds 13 (4.2 mg, tR = 16.8 min) and 34 (1.6 mg, tR = 15.6 min). Then, B5 was also purified using a preparative HPLC to give compounds 1 (3.1 mg, tR = 18.9 min), 6 (2.6 mg, tR = 18.8 min), 31 (2.7 mg, tR = 16.5 min) and 32 (6.5 mg, tR = 16.9 min). B7 was separated by a preparative HPLC to create compounds 33 (6.5 mg, tR = 18.3 min) and 36 (3.9 mg, tR = 17.8 min). B8 was purified by a preparative HPLC to yield compounds 35 (12.1 mg, tR = 19.8 min) and 37 (32.3 mg, tR = 19.2 min). B9 was applied to a preparative HPLC to give compounds 29 (5.2 mg, tR = 20.5 min) and 30 (12.8 mg, tR = 20.1 min). B11 was purified with a preparative HPLC to yield compounds 19 (4.2 mg, tR = 22.2 min), 20 (5.3 mg, tR = 23.1 min) and 21 (2.1 mg, tR = 23.3 min). Fraction C (20.7 g) was then eluted on an ODS column to yield 13 subfractions (C1-C13). One of these subfractions, C2, was further purified on a preparative HPLC. As a result, crops of compounds 2 (2.9 mg, tR = 13.5 min), 7 (1.4 mg, tR = 14.0 min), 12 (15.8 mg, tR = 14.8 min) and 27 (8.0 mg, tR = 11.5 min) were obtained. Two other subfractions (C8 and C10) were further applied to a preparative HPLC to afford compounds 8 (6.3 mg, tR = 20.9 min) and 3 (2.8 mg, tR = 22.9 min). On the other hand, fraction D (10.8 g) was eluted on an ODS column (MeOH-H2O, 10–100% MeOH) to obtain 12 subfractions (D1-D12). Subfraction D6 was purified using a preparative HPLC to give compounds 9 (9.0 mg, tR = 19.9 min), 10 (13.9 mg, tR = 20.0 min), 11 (10.8 mg, tR = 19.5 min), 15 (5.1 mg, tR = 18.8 min), 22 (20.6 mg,
was a bicyclic neomegastigmane, and a plausible biogenetic pathway for it was further
elucidated based on MS and NMR spectroscopic data and comparison with data reported
in this research, and five of them were new structures (1–3, 12, 29). Their structures were
elucidated based on MS and NMR spectroscopic data and comparison with data reported
in the literature [51]. The n-hexane fractions were then detected by GC-MS with a
DB-5 capillary column, and the absolute configuration of sugar components was confirmed
to be D-glucose, L-arabinofuranose and D-glucose in compounds 3, 12, and 29.

3.4. Characterization of Compounds 1–3, 12, 29

Diamegastigmane A (1): white amorphous powder; $[\alpha]_{D}^{20} = +11$ (c = 0.1, MeOH); HRESIMS
m/z 225.1489 [M+H]+ (calcd. for C13H21O3, m/z 225.1490); $^{1}H$-NMR (methanol-
$d_{4}$, 600 MHz) and $^{13}C$-NMR (methanol-$d_{4}$, 150 MHz), see Table 1.

Diamegastigmane B (2): white amorphous powder; $[\alpha]_{D}^{20} = +10$ (c = 0.1, MeOH); HRESIMS
m/z 485.3115 [2M+H]+ (calcd. for C26H45O6, m/z 485.3114); $^{1}H$-NMR (methanol-
$d_{4}$, 600 MHz) and $^{13}C$-NMR (methanol-$d_{4}$, 150 MHz), see Table 1.

Diamegastigmane C (3): white amorphous powder; $[\alpha]_{D}^{20} = +35$ (c = 0.1, MeOH); HRESIMS
m/z 493.2442 [M+H]+ (calcd. for C26H37O9, m/z 493.2437); $^{1}H$-NMR (methanol-
$d_{4}$, 600 MHz) and $^{13}C$-NMR (methanol-$d_{4}$, 150 MHz), see Table 1.

3,5,7-trihydroxychromone-3-O-$\alpha$-L-arabinofuranoside (12): yellow amorphous powder;
$[\alpha]_{D}^{20} = -166$ (c = 0.1, MeOH); HRESIMS m/z 327.0715 [M+H]+ (calcd. for C14H15O9, m/z
327.0716); $^{1}H$-NMR (methanol-$d_{4}$, 600 MHz) and $^{13}C$-NMR (methanol-$d_{4}$, 150 MHz), see
Table 2.

1-O-(Z)-coumaroyl-6-O-(E)-coumaroyl-$\beta$-D-glucopyranoside (29): Yellow amorphous
powder; $[\alpha]_{D}^{24} = -50$ (c = 0.3, MeOH); HRESIMS m/z 471.1286 [M-H]- (calcd. for C24H29O10,
m/z 471.1290); $^{1}H$-NMR (methanol-$d_{4}$, 600 MHz) and $^{13}C$-NMR (methanol-$d_{4}$, 150 MHz), see
Table 3.

3.5. Acid Hydrolysis of Compounds 3, 12 and 29

In order to determine the absolute configuration of monosaccharides in the new
compounds, the acid hydrolysis of compounds 3, 12 and 29 were performed according to
the previous literature [51]. The n-hexane fractions were then detected by GC-MS with a
DB-5 capillary column, and the absolute configuration of sugar components was confirmed
to be D-glucose, L-arabinofuranose and D-glucose in compounds 3, 12 and 29, respectively,
compared with standards.

3.6. $\alpha$-Glucosidase Inhibitory Assay

The $\alpha$-glucosidase inhibition assay was performed according to a previous report [52]
with a slight difference: the concentration of $\alpha$-glucosidase was diluted to 0.15 unit/mL.
The volume of $\alpha$-glucosidase added to the 96-well plate was 10 µL. Acarbose was used as the
positive control.

4. Conclusions

In summary, a detailed phytochemical investigation on the EtOAc partition of 70%
ethanol extract of Diaphagma juglandis Fructus was carried out to afford 37 constituents
in this research, and five of them were new structures (1–3, 12, 29). Their structures were
elucidated based on MS and NMR spectroscopic data and comparison with data reported
in the literature. Compounds 1–3 were new megastigmanes. Among them, compound 1
was a bicyclic neomegastigmane, and a plausible biogenetic pathway for it was further
discussed in this paper. Compound 12 was a new chrome with $\alpha$-L-arabinofuranoside.
Compound 29 was a new phenylpropanoid. The $\alpha$-glucosidase inhibition activity was also
investigated. Compounds 13, 16, 21 and 28 were found to be quite potent and most of
them were flavonoids, suggesting that flavonoids might be the main bioactive substances
contributing to the α-glucosidase inhibitory activity of Diaphragma juglandis Fructus. These findings also revealed that these compounds could be target compounds for the development of new antidiabetic agents.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules27103045/s1. A scheme of extraction and isolation (Figure S1), spectroscopic data for compounds 1–3, 12 and 29 (Figures S2–S39), 13C-NMR spectra of compounds 4–11, 13–28, 30–37 (Figures S40–S71) are available as Supporting Information.

Author Contributions: J.T. and Y.C. carried out the extraction and purification process. S.W. and J.L. performed the whole experiment process as assistants. H.R. contributed to the revision of the paper. Y.Q. assisted with the α-glucosidase inhibitory assay. Q.L. contributed to the elucidation of the chemical structures. Y.W. designed the whole research plan and wrote the paper. All authors have read and agreed to the published version of the manuscript.

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