

Article

Phytochemical Study of Aerial Parts of *Leea asiatica*

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Abstract: *Leea asiatica* (L.) Ridsdale (Leeaceae) is found in tropical and subtropical countries and has historically been used as a traditional medicine in local healthcare systems. Although *L. asiatica* extracts have been found to possess anthelmintic and antioxidant-related nephroprotective and hepatoprotective effects, little attention has been paid toward the investigation of phytochemical constituents of this plant. In the current study, phytochemical analysis of isolates from *L. asiatica* led to the identification of 24 compounds, including a novel phenolic glucoside, seven triterpenoids, eight flavonoids, two phenolic glycosides, four diglycosidic compounds, and two miscellaneous compounds. The phytochemical structures of the isolates from *L. asiatica* were elucidated using spectroscopic analyses including 1D- and 2D-NMR and ESI-Q-TOF-MS. The presence of triterpenoids and flavonoids supports the evidence for anthelmintic and antioxidative effects of *L. asiatica*.

Keywords: *Leea asiatica*; leeaceae; phytochemistry; triterpenoids; phenolic glycosides

1. Introduction

Plant species of the genus Leeaceae (*Leea*) are widely distributed among tropical and subtropical regions, including Eastern Africa, Australia, China, India, Indonesia, Laos, Malaysia, Myanmar, and Thailand [1,2]. Around 70 different species of the genus *Leea* (L.) are found in these regions, with some being used in local traditional healthcare systems to treat bone fractures, liver disorders, physical wounds, skin diseases, and worm infections [1]. Various biological studies have reported the antibacterial, antioxidative, anthelmintic, cytotoxic, hepatoprotective, and nephroprotective effects of the *Leea* species. Several phytochemicals, including coumarin, essential oils, flavonoids, hydrocarbons, and triterpenoids have been determined from the extracts of diverse *Leea* species, such as *L. thorelii* [1,3], *L. indica* [4–9], *L. macrophylla* [10,11], and *L. guineense* [12,13]. Although several *Leea* species have been evaluated from both a biological and phytochemical perspective, relatively few studies have included *L. asiatica* (L.) Ridsdale in their analyses. *Leea asiatica* has also been used as a folk medicine, especially in India, to treat worm infection, bone fracture, liver disorder, and oxidative stress-related diseases. Up to date, three published reports have described the biological effects of *L. asiatica* extracts, including anthelmintic and antioxidant-related nephroprotective and hepatoprotective activities [14–16], and no phytochemical study on this species has been attempted yet even though *L. asiatica* has been used as a traditional medicine, as have other *Leea* species. The identification of the phytochemicals of herbal medicine is very important because it can be used as a primary data for the prediction of biological effects, safety information, and clarification of medicinal use. From this point of view, the current study was designed to identify chemical constituents of *L. asiatica* and to provide their spectroscopic information. We describe here a novel compound (1) along with seven triterpenoids (2–8), eight flavonoids (9–16), two phenolic glucosides (17–18), four diglycosidic compounds (19–22), and two miscellaneous compounds (23–24) (Figure 1).

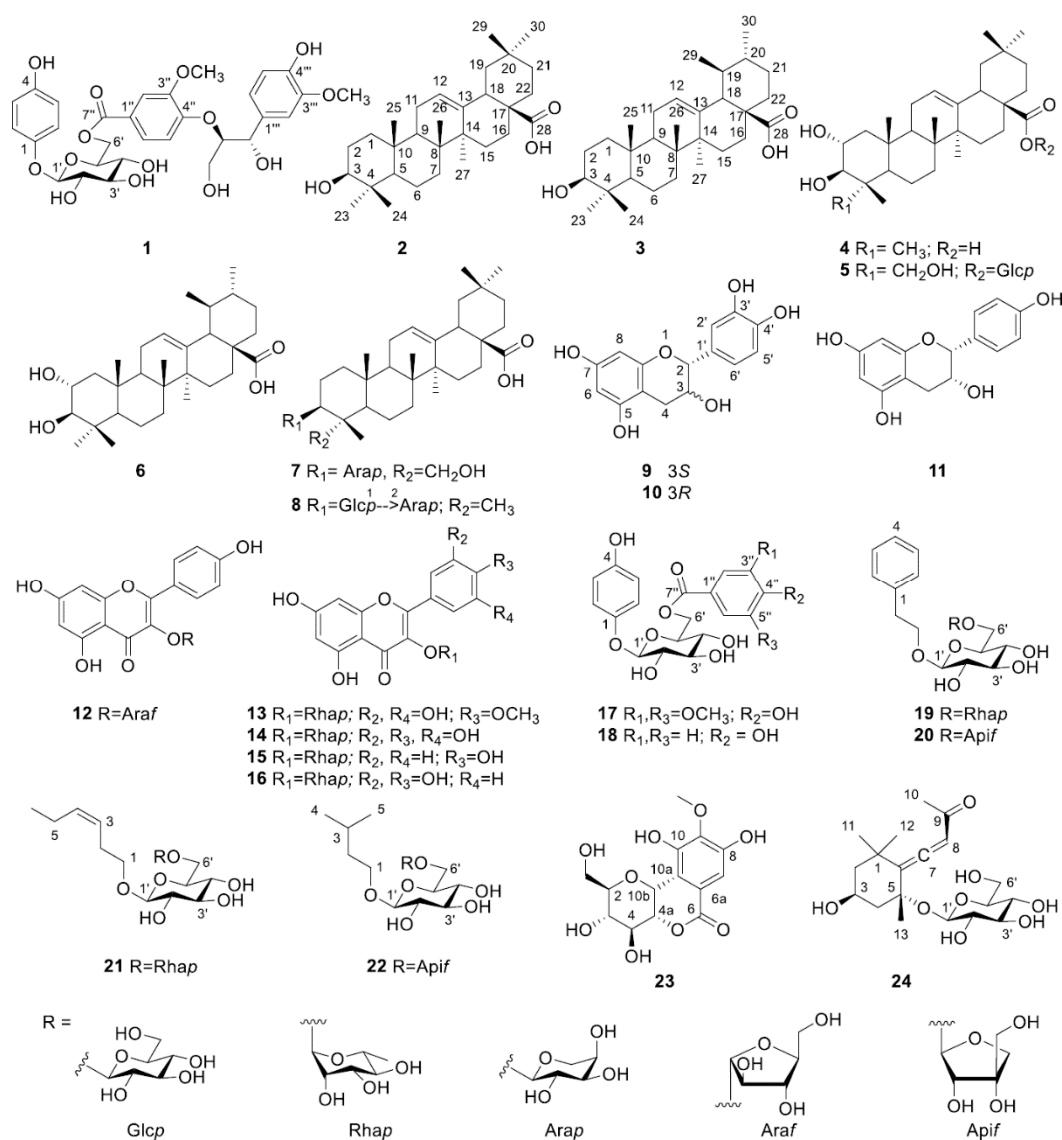


Figure 1. The chemical structures of compounds 1–24 from the aerial parts of *Leea asiatica*.

2. Results and Discussion

2.1. Elucidation of Chemical Structures of Compounds 1–24

The molecular formula of compound 1 was identified as C₃₀H₃₄O₁₄, according to its ESI-Q-TOF-MS spectrum, which showed the quasi-molecular ion peak at m/z 617.1884 [M – H][–] (calcd. for C₃₀H₃₃O₁₄, 617.1870). The ¹H-NMR spectrum of compound 1 showed resonances characteristic for a 1,4-disubstituted benzene ring [δ_{H} 6.91 (2H, d, J = 9.0 Hz, H-2, 6), 6.56 (2H, d, J = 9.0 Hz, H-3, 5)], an anomeric proton of a sugar group at δ_{H} 4.73 (1H, d, J = 7.4 Hz, H-1'), two sets of 1,3,4-trisubstituted benzene moieties [δ_{H} 7.57 (1H, dd, J = 8.5, 2.0 Hz, H-6''), 7.51 (1H, d, J = 2.0 Hz, H-2''), and 7.06 (1H, d, J = 8.5 Hz, H-5''); δ_{H} 7.07 (1H, o, H-2'''), 6.87 (1H, dd, J = 8.1, 2.2 Hz, H-6'''), and 6.71 (1H, d, J = 8.1 Hz, H-5''')], two oxygenated methine signals at δ_{H} 4.84 (1H, o, H-7''') and 4.64 (1H, m, H-8'''), a hydroxylated methylene resonance at δ_{H} 3.86 (2H, brd, J = 4.9 Hz, H-9'''), and two methoxy signals [δ_{H} 3.79 (3H, s, 3''-OCH₃) and 3.80 (3H, s, 3'''-OCH₃)]. Exhaustive 1D- and 2D-NMR (¹H-¹H COSY, HSQC, and HMBC) interpretations suggested that compound 1 contained a guaiacylglycerol 8-yl, a 3-methoxy-4-hydroxyphenoxy, a 4-hydroxy-benzene, and a β -glucopyranosyl moiety, as shown in Figure 1. The sugar unit was identified as D-glucose

by acid hydrolysis. The connectivity of each functional group was established using the HMBC spectrum. Crossed peaks were observed at δ_{H} 4.73 (H-1')/ δ_{C} 152.3 (C-1), δ_{H} 4.68, 4.37 (H-6'a and H-6'b)/ δ_{C} 167.7 (C-7''), and δ_{H} 4.64 (H-8''')/ δ_{C} 154.2 (C-4'') (Figure 2a). The 7''',8'''-erythro configuration of compound 1 was deduced from the $\Delta\delta_{\text{C}8'''.\text{C}7''}$ value (11.0 ppm), and a negative Cotton effect at 229 nm in its circular dichroism (CD) spectrum indicated the 8R configuration, according to the findings of previous reports (Figure 2b) [17,18]. Based on the spectroscopic evidence (Supplementary Information SI 7–SI 8), and searching the confirmed structure of compound 1 through Scifinder® and Reaxys® databases, compound 1 was identified as a new compound with a chemical structure of 4-hydroxyphenol- β -D-[6-O-[4-O-(7S,8R-guaiacylglycerol-8-yl)-3-methoxybenzoyl]]- β -D-glucopyranoside. The molecular structure of 1 was very similar to that of (–)-4-hydroxy-3-methoxyphenol β -D-[6-O-[4-O-(7S,8R)-(4-hydroxy-3-methoxyphenylglycerol-8-yl)-3-methoxybenzoyl]]-glucopyranoside, which was determined in a previous phytochemical study [16]. The comparison of ^1H - and ^{13}C -NMR data of both compounds was described in Supplementary Information SI 8.

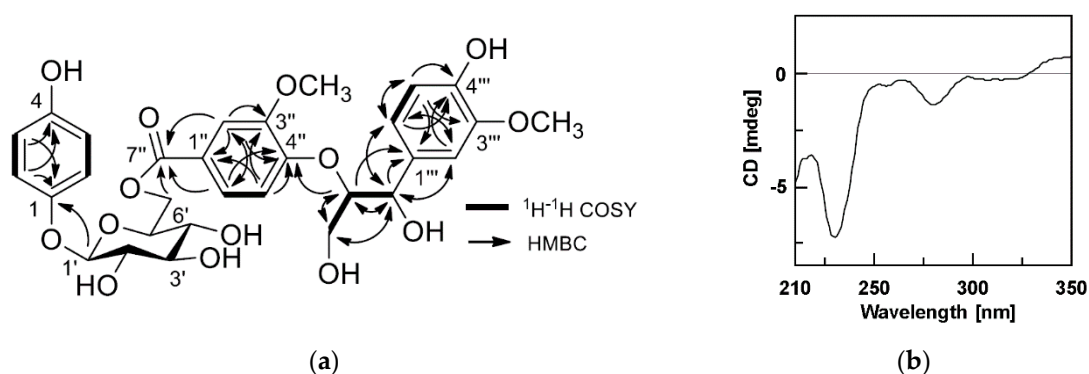


Figure 2. (a) ^1H - ^1H COSY and HMBC correlation of compound 1; (b) circular dichroism (CD) spectrum of compound 1.

The following known compounds were also identified: Oleanolic acid (2) [19], ursolic acid (3) [19], maslinic acid (4) [20,21], chebuloside ii (5) [22,23], corosolic acid (6) [21], hederagenin-3-O-arabinopyranoside (7) [24], oleanolic acid 3-O-glucopyranosyl-(1→2)-arabinopyranoside (8) [25], (+)-catechin (9) [26], (–)-epicatechin (10) [26], (–)-epiafzelechin (11) [27], juglanin (12) [28], mearnsenin 3-O-rhamnopyranoside (13) [29], myricitrin (14) [30], afzelin (15) [30], quercitrin (16) [30], 4-hydroxyphenol-[6-O-(4''-hydroxy-3'',5''-dimethoxy-benzoate)]- β -D-glucopyranoside (17) [31], breynioside A (18) [32], phenylethyl-rutinoside (19) [33], icaraside D1 (20) [34], hexenyl-rutinoside (21) [35], everlastoside C (22) [36], bergenin (23) [37], and citroside A (24) [38]. To the best of our knowledge, compounds 2 [9] (*L. macrophylla*), 3 (*L. indica*) [5], 16 [3,5,9] (*L. indica* and *L. thorelii*), 9, 10, 14, 16, and 24 (*L. indica* and *L. thorelii*) [3] have been previously isolated from the several other *Leea* species, whereas compounds 4–8, 11–13, 15, and 17–22 were here isolated from the *Leea* species, especially from *L. asiatica*, for the first time. However, the phytochemical profile of the plant is mainly affected by the genetic and environmental factors (e.g., soil, climate conditions, and seasonality) during plant growth, extraction, and isolation method. This phytochemical study does not represent all chemical profiles of *L. asiatica*. Therefore, further phytochemical study on *L. asiatica* from different regions should be performed to achieve a full understanding of the chemical composition of *L. asiatica*.

As mentioned in the Introduction, *L. asiatica* possessed anthelmintic [14] and antioxidative activity-related nephroprotective and hepatoprotective effects [15,16]. The current study demonstrated the presence of triterpenoids, including oleanolic acid, ursolic acid, the representative pentacyclic triterpenes, and their derivatives (1–8). The anthelmintic activity of *L. asiatica* is thought to be exerted by triterpenoids because several reports demonstrated that oleanolic acid and ursolic acid possessed anthelmintic activity [39,40], and saponins were also associated with the ovicidal action of the plant extract [41]. Thus, this study supports the evidence for clarifying the anthelmintic effect of *L.*

asiatica. The antioxidant properties of the *L. asiatica* extract were well-proven in previous literatures and, especially the ethyl acetate-soluble extract, showed the most potent antioxidative effects [16]. In this study, eight flavonoids (9–16) were determined specifically from the ethyl acetate-soluble extract (Supplementary Information SI 9), which indicated that flavonoids were enriched in an ethyl acetate-soluble extract. Therefore, it is suggested that the antioxidant potency of the ethyl acetate-soluble extract of *L. asiatica* was directly related to the flavonoid contents because flavonoids such as catechins, quercetin, kaempferol, and myricetin and their derivatives are the most important natural antioxidants and exhibit numerous antioxidant-related beneficial effects [42–46]. Consequently, this study provides reasonable evidence for previous biological effects of *L. asiatica* as well as its phytochemical profile.

2.2. Characterisation of Compounds 1–24

4-Hydroxyphenol-[6-O-[4-O-(7S,8R-guaiacylglycerol-8-yl)-3-methoxybenzoyl]]-β-D-glucopyranoside (1): Brown amorphous powder; ESI-Q-TOF-MS: $m/z = 617.1884$ [M – H][−] (calcd. for C₃₀H₃₃O₁₄, 617.1870); [α]_D²² −4.4 (*c* = 0.05, MeOH); CD(MeOH) Δε −5.35 (229 nm), −0.3 (252 nm), −0.14 (264 nm), −1.02 (281 nm), 0.05 (298 nm); UV (MeOH) λ_{max} (log ε) 204 (6.15), 219 (5.90), 266 (5.54), 285 (5.46) nm; ¹H-NMR (500 MHz, MeOH-*d*₄): δ 7.57 (1H, dd, *J* = 8.5, 2.0 Hz, H-6''), 7.51 (1H, d, *J* = 2.0 Hz, H-2''), 7.07 (1H, o, H-2'''), 7.06 (1H, d, *J* = 8.5 Hz, H-5''), 6.91 (2H, d, *J* = 9.0 Hz, H-2, 6), 6.87 (1H, dd, *J* = 8.1, 2.2 Hz, H-6'''), 6.71 (1H, d, *J* = 8.1 Hz, H-5'''), 6.56 (2H, d, *J* = 9.0 Hz, H-3, 5), 4.84 (1H, o, H-7'''), 4.73 (1H, d, *J* = 7.4 Hz, H-1'), 4.68 (1H, dd, *J* = 11.7, 2.1 Hz, H-6'a), 4.64 (1H, m, H-8'''), 4.37 (1H, dd, *J* = 11.7, 7.6 Hz, H-6'b), 3.86 (1H, brd, *J* = 4.9 Hz, H-9'''), 3.80 (3H, s, 3'''-OCH₃), 3.79 (3H, s, 3''-OCH₃), 3.71 (1H, m, H-5'), 3.45 (1H, o, H-3'), 3.44 (1H, o, H-2'), 3.39 (1H, brt, H-4'), m: Multiplet, o: Resonance was overlapped; ¹³C-NMR (125 MHz, MeOH-*d*₄): δ 167.7 (C-7''), 154.2 (C-4''), 154.0 (C-4), 152.3 (C-1), 151.2 (C-3''), 148.8 (C-3'''), 147.2 (C-4'''), 133.9 (C-1'''), 124.8 (C-6''), 124.2 (C-1''), 121.4 (C-6'''), 119.6 (C-2), 119.6 (C-6), 116.7 (C-3), 116.7 (C-5), 116.4 (C-5''), 115.7 (C-5'''), 114.5 (C-2''), 112.2 (C-2'''), 103.7 (C-1'), 85.3 (C-8'''), 78.1 (C-3'), 75.6 (C-5'), 75.1 (C-2'), 74.3 (C-7'''), 72.2 (C-4'), 65.4 (C-6'), 62.6 (C-9'''), 56.7 (3''-OCH₃), 56.5 (3'''-OCH₃).

Oleanolic acid (2): White amorphous powder; ESI-Q-TOF-MS: m/z 455.3532 [M – H][−] (calcd. for C₃₀H₄₇O₃, 455.3525); ¹H-NMR (500 MHz, pyridine-*d*₅): δ 5.52 (1H, s, H-12), 3.47 (1H, dd, *J* = 10.6, 6.4 Hz, H-3), 1.31 (3H, s, H-27), 1.27 (3H, s, H-23), 1.05 (6H, s, H-26, H-30), 1.03 (3H, s, H-24), 0.97 (3H, s, H-29), 0.92 (3H, s, H-25); ¹³C-NMR (125 MHz, pyridine-*d*₅): δ 180.6 (C-28), 145.2 (C-13), 122.9 (C-12), 78.4 (C-3), 56.1 (C-5), 48.5 (C-9), 47.0 (C-17), 46.8 (C-19), 42.5 (C-14), 42.4 (C-18), 40.1 (C-8), 39.7 (C-4), 39.3 (C-1), 37.7 (C-10), 34.6 (C-21), 33.6 (C-22, 29), 33.5 (C-7), 31.3 (C-20), 29.1 (C-23), 28.6 (C-15), 28.4 (C-2), 26.5 (C-27), 24.2 (C-11), 24.1 (C-16), 23.2 (C-30), 19.1 (C-6), 17.8 (C-26), 16.9 (C-24), 15.9 (C-25).

Ursolic acid (3): White amorphous powder; ESI-Q-TOF-MS: m/z 455.3529 [M – H][−] (calcd. for C₃₀H₄₇O₃, 455.3525); ¹H-NMR (500 MHz, pyridine-*d*₅): δ 5.51 (1H, s, H-12), 3.48 (1H, dd, *J* = 10.4, 5.7 Hz, H-3), 1.27 (6H, s, H-23, 26), 1.25 (3H, s, H-27), 1.05 (3H, s, H-24), 1.03 (3H, s, H-29), 0.98 (3H, s, H-30), 0.92 (3H, s, H-25); ¹³C-NMR (125 MHz, pyridine-*d*₅): δ 180.4 (C-28), 139.6 (C-13), 125.9 (C-12), 78.4 (C-3), 56.1 (C-5), 53.9 (C-18), 48.4 (C-9), 48.4 (C-17), 42.8 (C-14), 40.3 (C-8), 39.7 (C-4, 19, 20), 39.4 (C-1), 37.7 (C-10), 37.6 (C-22), 33.9 (C-7), 31.4 (C-21), 29.1 (C-23), 29.0 (C-15), 28.4 (C-2), 25.3 (C-16), 24.2 (C-27), 23.9 (C-11), 21.7 (C-30), 19.1 (C-6), 17.8 (C-26), 16.9 (C-29), 16.0 (C-24), 14.6 (C-25).

Maslinic acid (4): White amorphous powder; ESI-Q-TOF-MS: m/z 471.3477 [M – H][−] (calcd. for C₃₀H₄₇O₄, 471.3474); ¹H-NMR (500 MHz, pyridine-*d*₅): δ 5.49 (1H, s, H-12), 4.12 (1H, m, H-2), 3.42 (1H, d, *J* = 9.4 Hz, H-3), 1.30 (3H, s, H-29), 1.29 (3H, s, H-23), 1.23 (3H, s, H-27), 1.10 (3H, s, H-26), 1.04 (3H, s, H-30), 0.96 (3H, s, H-25); ¹³C-NMR (125 MHz, pyridine-*d*₅): δ 180.7 (C-28), 145.3 (C-13), 122.7 (C-12), 84.1 (C-3), 68.9 (C-2), 56.2 (C-5), 48.5 (C-8), 48.5 (C-9), 48.1 (C-1), 47.0 (C-17), 46.8 (C-19), 42.5 (C-14), 42.3 (C-18), 40.2 (C-4), 38.9 (C-10), 34.6 (C-21), 33.6 (C-7), 33.5 (C-22, 29), 31.3 (C-20), 29.7 (C-23), 28.6 (C-15), 26.5 (C-27), 24.3 (C-30), 24.1 (C-11), 24.0 (C-16), 19.2 (C-6), 18.0 (C-26), 17.8 (C-25), 17.2 (C-24).

Chebuloside ii (5): White amorphous powder; ESI-Q-TOF-MS: m/z 689.3886 $[M + Na]^+$ (calcd. for $C_{36}H_{58}O_{11}Na$, 689.3877); 1H -NMR (500 MHz, pyridine- d_5): δ 6.34 (1H, d, $J = 8.1$ Hz, H-1'), 5.55 (1H, t, $J = 3.4$ Hz, H-12), 5.12 (1H, s, H-6), 4.44 (2H, m, H-2, H-23), 4.26 (1H, m, H-3), 4.09 (1H, d, $J = 10.6$ Hz, H-23), 1.84 (3H, s, H-26), 1.79 (3H, s, H-23), 1.77 (3H, s, H-25), 1.22 (3H, s, H-27), 0.89 (6H, s, H-29, H-30); ^{13}C -NMR (125 MHz, pyridine- d_5): δ 176.7 (C-28), 143.8 (C-13), 123.4 (C-12), 96.2 (C-1'), 79.1 (C-3'), 78.7 (C-3, 5'), 74.5 (C-2'), 71.5 (C-4'), 69.4 (C-2), 67.9 (C-6), 66.6 (C-23), 62.5 (C-6'), 50.1 (C-1), 49.2 (C-9), 49.1 (C-5, 19), 47.3 (C-17), 43.2 (C-4, 14), 42.2 (C-18), 41.5 (C-7, 8), 38.6 (C-10), 34.4 (C-21), 33.4 (C-29), 32.9 (C-22), 31.1 (C-20), 28.6 (C-15), 26.5 (C-27), 23.9 (C-16, 30), 23.9 (C-30), 23.2 (C-11), 19.4 (C-26), 19.2 (C-25), 16.4 (C-24).

Corosolic acid (6): White amorphous powder; ESI-Q-TOF-MS: m/z 471.3483 $[M - H]^-$ (calcd. for $C_{30}H_{47}O_4$, 471.3474); 1H -NMR (500 MHz, pyridine- d_5): δ 5.48 (1H, s, H-12), 4.12 (1H, m, H-2), 3.42 (1H, d, $J = 9.4$ Hz, H-3), 1.30 (3H, s, H-29), 1.23 (3H, s, H-27), 1.10 (3H, s, H-24), 1.06 (3H, s, H-25), 1.00 (3H, d, $J = 6.3$ Hz, H-30), 0.97 (3H, d, $J = 6.3$ Hz, H-29); ^{13}C -NMR (125 MHz, pyridine- d_5): δ 180.4 (C-28), 139.7 (C-13), 125.8 (C-12), 84.1 (C-3), 68.9 (C-2), 56.2 (C-5), 53.9 (C-18), 48.4 (C-1, 17), 48.3 (C-9), 42.9 (C-14), 40.3 (C-8), 40.2 (C-4), 39.8 (C-20), 39.7 (C-19), 38.8 (C-10), 37.8 (C-22), 33.8 (C-7), 31.4 (C-21), 29.7 (C-23), 29.0 (C-15), 25.2 (C-16), 24.2 (C-27), 24.1 (C-11), 21.7 (C-30), 19.2 (C-6), 18.0 (C-24), 17.8 (C-26, 29), 17.3 (C-25).

Hederagenin-3-O-arabinopyranoside (7): White amorphous powder; ESI-Q-TOF-MS: m/z 663.3887 $[M - H]^-$ (calcd. for $C_{35}H_{55}O_8$, 603.3897); 1H -NMR (500 MHz, pyridine- d_5): δ 5.49 (1H, s, H-12), 5.00 (1H, d, $J = 7.1$ Hz, H-1'), 4.31 (2H, m, H-3, H-23a), 3.75 (1H, d, $J = 10.4$ Hz, H-23b), 1.25 (3H, s, H-27), 1.04 (3H, s, H-26), 1.02 (3H, s, H-30), 0.96 (3H, s, H-25), 0.94 (6H, s, H-24, H-29); ^{13}C -NMR (125 MHz, pyridine- d_5): δ 180.7 (C-28), 145.2 (C-13), 122.8 (C-12), 107.0 (C-1'), 82.2 (C-3), 75.0 (C-2'), 73.4 (C-3'), 70.1 (C-4'), 67.3 (C-5'), 64.8 (C-23), 48.5 (C-9), 47.9 (C-5), 47.0 (C-17), 46.8 (C-19), 43.8 (C-4), 42.5 (C-14), 42.3 (C-18), 40.1 (C-8), 39.1 (C-1), 37.3 (C-10), 34.6 (C-21), 33.6 (C-22, 29), 33.2 (C-7), 31.3 (C-20), 28.7 (C-15), 26.5 (C-2, 27), 24.2 (C-11), 24.1 (C-16), 24.0 (C-30), 18.5 (C-6), 17.8 (C-26), 16.4 (C-25), 13.9 (C-24).

Oleanolic acid 3-O-glucopyranosyl-(1→2)-arabinopyranoside (8): White amorphous powder; ESI-Q-TOF-MS: m/z 749.4456 $[M - H]^-$ (calcd. for $C_{41}H_{65}O_{12}$, 749.4476); 1H -NMR (500 MHz, pyridine- d_5): δ 5.49 (1H, s, H-12), 5.22 (1H, d, $J = 7.7$ Hz, H-1''), 4.99 (1H, d, $J = 5.9$ Hz, H-1'), 3.22 (1H, dd, $J = 11.6, 4.2$ Hz, H-3), 1.30 (3H, s, H-27), 1.25 (3H, s, H-23), 1.06 (3H, s, H-24), 1.03 (6H, s, H-26, H-30), 0.97 (3H, s, H-29), 0.84 (3H, s, H-25); ^{13}C -NMR (125 MHz, pyridine- d_5): δ 180.6 (C-28), 145.2 (C-13), 122.8 (C-12), 106.4 (C-6'), 105.2 (C-1'), 89.1 (C-3), 81.4 (C-2'), 78.5 (C-2'', 4''), 76.8 (C-1''), 73.8 (C-3'), 71.8 (C-3''), 68.6 (C-4'), 65.3 (C-5'), 62.9 (C-5''), 56.1 (C-5), 48.3 (C-9), 46.8 (C-17, 19), 42.5 (C-14), 42.3 (C-18), 40.0 (C-8), 39.8 (C-4), 39.0 (C-1), 37.3 (C-10), 34.5 (C-21), 33.6 (C-7, 22, 29), 31.3 (C-20), 28.6 (C-15, 23), 26.5 (C-2, 27), 24.1 (C-16), 24.0 (C-11, 30), 18.8 (C-6), 17.7 (C-26), 17.1 (C-24), 15.8 (C-25).

(+)-Catechin (9): Brown amorphous solid; ESI-Q-TOF-MS: m/z 291.0858 $[M+H]^+$ (calcd. for $C_{15}H_{15}O_6$, 291.0869); 1H -NMR (500 MHz, DMSO- d_6): δ 6.84 (1H, s, H-2'), 6.76 (1H, d, $J = 8.0$ Hz, H-5'), 6.72 (1H, d, $J = 8.0$ Hz, H-6'), 5.93 (1H, d, $J = 1.9$ Hz, H-8), 5.85 (1H, d, $J = 1.9$ Hz, H-6), 4.56 (1H, d, $J = 7.5$ Hz, H-2), 3.97 (1H, dd, $J = 13.2, 7.6$ Hz, H-3), 2.85 (1H, dd, $J = 16.1, 5.3$ Hz, H-4a), 2.50 (1H, dd, $J = 16.1, 8.1$ Hz, H-4b); ^{13}C -NMR (125 MHz, DMSO- d_6): δ 156.4 (C-7), 156.1 (C-5), 155.3 (C-9), 144.8 (C-3', 4'), 130.5 (C-1'), 118.4 (C-6'), 115.0 (C-5'), 114.5 (C-2'), 99.0 (C-10), 95.0 (C-6), 93.8 (C-8), 80.9 (C-2), 66.3 (C-3), 27.8 (C-4).

(-)-Epicatechin (10): Brown amorphous solid; ESI-Q-TOF-MS: m/z 291.0860 $[M+H]^+$ (calcd. for $C_{15}H_{15}O_6$, 291.0869); 1H -NMR (500 MHz, DMSO- d_6): δ 6.88 (1H, d, $J = 1.6$ Hz, H-2'), 6.66 (1H, d, $J = 8.1$ Hz, H-5'), 6.64 (1H, dd, $J = 8.1, 1.6$ Hz, H-6'), 5.89 (1H, d, $J = 2.3$ Hz, H-6), 5.85 (1H, d, $J = 2.3$ Hz, H-8), 4.73 (1H, s, H-2), 4.00 (1H, s, H-3), 2.67 (1H, dd, $J = 16.3, 4.5$ Hz, H-4a), 2.49 (1H, dd, $J = 16.3, 3.4$ Hz, H-4b); ^{13}C -NMR (125 MHz, DMSO- d_6): δ 156.5 (C-5), 156.2 (C-7), 155.7 (C-9), 144.4 (C-3', 4'), 130.5 (C-1'), 117.9 (C-6'), 114.8 (C-5'), 114.7 (C-2'), 98.4 (C-10), 95.0 (C-6), 94.0 (C-8), 78.0 (C-2), 64.8 (C-3), 28.1 (C-4).

(-)-*Epiapfzelechin* (**11**): Yellow amorphous powder; ESI-Q-TOF-MS: m/z 297.0735 [M + Na]⁺ (calcd. for C₁₅H₁₄O₅Na, 297.0739); ¹H-NMR (500 MHz, DMSO-*d*₆): δ 7.22 (2H, d, *J* = 8.5 Hz, H-2', 6'), 6.71 (2H, d, *J* = 8.5 Hz, H-3', 5'), 5.89 (1H, d, *J* = 2.3 Hz, H-8), 5.72 (1H, d, *J* = 2.3 Hz, H-6), 4.80 (1H, s, H-2), 4.02 (1H, dd, *J* = 8.3, 4.5 Hz, H-3), 2.67 (1H, m, H-4a), 2.46 (1H, m, H-4b); ¹³C-NMR (125 MHz, DMSO-*d*₆): δ 156.5 (C-7), 156.2 (C-5, 9), 155.7 (C-4'), 129.9 (C-1'), 128.2 (C-2', 6'), 114.3 (C-3', 5'), 98.4 (C-10), 95.0 (C-8), 94.0 (C-6), 77.9 (C-2), 64.7 (C-3), 28.1 (C-4).

Juglanin (**12**): Yellow amorphous powder; ESI-Q-TOF-MS: m/z 441.0796 [M + Na]⁺ (calcd. for C₂₀H₁₈O₁₀Na, 441.0798); ¹H-NMR (500 MHz, DMSO-*d*₆): δ 7.96 (2H, d, *J* = 8.7 Hz, H-2', 6'), 6.92 (2H, d, *J* = 8.7 Hz, H-3', 5'), 6.40 (1H, d, *J* = 1.6 Hz, H-8), 6.21 (1H, d, *J* = 1.6 Hz, H-6), 5.50 (1H, s, H-1''); ¹³C-NMR (125 MHz, DMSO-*d*₆): δ 180.0 (C-4), 166.2 (C-7), 163.2 (C-5), 161.7 (C-4'), 159.5 (C-9), 158.7 (C-2), 135.1 (C-3), 132.1 (C-2', 6'), 122.9 (C-1'), 116.6 (C-3', 5'), 109.8 (C-1''), 105.8 (C-10), 100.0 (C-6), 94.9 (C-8), 88.1 (C-4''), 83.5 (C-2''), 78.8 (C-3''), 62.7 (C-5'').

Mearnsetin 3-O-rhamnopyranoside (**13**): Yellow amorphous powder; ESI-Q-TOF-MS: m/z 501.1012 [M + Na]⁺ (calcd. for C₂₂H₂₂O₁₂, 501.1009); ¹H-NMR (500 MHz, DMSO-*d*₆): δ 6.81 (2H, s, H-2', 6'), 6.36 (1H, brs, H-6), 6.19 (1H, brs, H-8), 5.15 (1H, brs, H-1''), 3.98 (1H, dd, 3.5, 1.2 Hz, H-2''), 3.74 (1H, s, 4'-OCH₃), 3.51 (1H, dd, *J* = 8.4, 3.0 Hz, H-3''), 3.32 (1H, m, H-5''), 3.15 (1H, m, H-4''), 0.82 (3H, d, *J* = 5.4 Hz, H-6''); ¹³C-NMR (125 MHz, DMSO-*d*₆): δ 177.7 (C-4), 164.9 (C-7), 161.3 (C-5), 157.1 (C-9), 156.5 (C-2), 150.7 (C-3', 5'), 137.7 (C-4'), 134.8 (C-3), 124.8 (C-1'), 108.1 (C-2', 6'), 103.9 (C-10), 102.1 (C-1''), 98.9 (C-6), 93.7 (C-8), 71.1 (C-4''), 70.5 (C-3''), 70.3 (C-2''), 70.0 (C-5''), 59.7 (4'-OCH₃), 17.4 (C-6'').

Myricitrin (**14**): Yellow amorphous powder; ESI-Q-TOF-MS: m/z 487.0852 [M + Na]⁺ (calcd. for C₂₁H₂₀O₁₂, 487.0852); ¹H-NMR (500 MHz, DMSO-*d*₆): δ 6.90 (2H, s, H-2', 6'), 6.38 (1H, d, *J* = 1.9 Hz, H-8), 6.21 (1H, d, *J* = 1.9 Hz, H-6), 5.21 (1H, d, *J* = 1.0 Hz, H-1''), 3.99 (1H, brs, H-2''), 3.57 (1H, dd, *J* = 9.2, 3.0 Hz, H-3''), 3.40 (1H, m, H-5''), 3.17 (1H, m, H-4'') 0.86 (3H, d, *J* = 6.2 Hz, H-6''); ¹³C-NMR (125 MHz, DMSO-*d*₆): δ 177.7 (C-4), 164.2 (C-7), 161.2 (C-5), 157.4 (C-2), 156.3 (C-9), 145.7 (C-3', 5'), 136.4 (C-4'), 134.2 (C-3), 119.5 (C-1'), 107.8 (C-2', 6'), 103.9 (C-10), 101.9 (C-1''), 98.6 (C-6), 93.4 (C-8), 71.2 (C-4''), 70.5 (C-5''), 70.3 (C-3''), 69.9 (C-2''), 17.5 (C-6'').

Afzelin (**15**): Yellow amorphous powder; ESI-Q-TOF-MS: m/z 455.0954 [M + Na]⁺ (calcd. for C₂₁H₂₀O₁₀, 455.0954); ¹H-NMR (500 MHz, DMSO-*d*₆): δ 7.75 (2H, d, *J* = 8.7 Hz, H-2', 6'), 6.90 (2H, d, *J* = 8.7 Hz, H-3', 5'), 6.33 (1H, s, H-8), 6.14 (1H, s, H-6), 5.29 (1H, s, H-1''), 3.97 (1H, brs, H-2''), 3.47 (1H, dd, *J* = 9.0, 2.9 Hz, H-3''), 3.38 (1H, o, H-5''), 3.13 (1H, t, *J* = 9.2 Hz, H-4''), 0.79 (3H, d, *J* = 6.0 Hz, H-6''); ¹³C-NMR (125 MHz, DMSO-*d*₆): δ 177.4 (C-4), 164.7 (C-7), 161.2 (C-5), 159.9 (C-4'), 158.8 (C-9), 156.6 (C-2), 134.0 (C-3), 130.5 (C-2', 6'), 120.5 (C-1'), 115.3 (C-3', 5'), 104.3 (C-10), 101.7 (C-1''), 99.0 (C-6), 93.9 (C-8), 70.5 (C-3''), 70.3 (C-2''), 70.1 (C-4''), 70.0 (C-5''), 17.4 (C-6'').

Quercitrin (**16**): Yellow amorphous powder; ESI-Q-TOF-MS: m/z 447.0931 [M - H]⁻ (calcd. for C₂₁H₁₉O₁₁, 447.0927); ¹H-NMR (500 MHz, DMSO-*d*₆): δ 7.30 (1H, d, *J* = 2.1 Hz, H-2'), 7.26 (1H, dd, *J* = 8.3, 2.1 Hz, H-6'), 6.87 (1H, d, *J* = 8.3 Hz, H-5'), 6.38 (1H, s, H-6), 6.20 (1H, s, H-8), 5.27 (1H, s, H-1''), 3.99 (1H, brs, H-2''), 3.52 (1H, dd, *J* = 9.1, 3.3 Hz, H-3''), 3.40 (1H, o, H-5''), 3.16 (1H, t, *J* = 9.4 Hz, H-4''), 0.83 (3H, d, *J* = 6.1 Hz, H-6''); ¹³C-NMR (125 MHz, DMSO-*d*₆): δ 177.6 (C-4), 164.7 (C-7), 161.2 (C-5), 157.1 (C-9), 156.4 (C-2), 148.5 (C-4'), 145.2 (C-3'), 134.1 (C-3), 121.0 (C-6'), 120.6 (C-1'), 115.5 (C-5'), 115.4 (C-2'), 103.9 (C-10), 101.7 (C-1''), 98.8 (C-6), 93.6 (C-8), 71.1 (C-4''), 70.5 (C-3''), 70.3 (C-2''), 70.0 (C-5''), 17.4 (C-6'').

4-Hydroxyphenol-[6-O-(4'-hydroxy-3'',5''-dimethoxy-benzoate)]-β-D-glucopyranoside(**17**): Brown amorphous solid; ESI-Q-TOF-MS m/z 475.1217 [M+H]⁺ (calcd. for C₂₁H₂₅O₁₁, 475.1216); ¹H-NMR (500 MHz, MeOH-*d*₄): δ 7.35 (2H, s, H-2'', 6''), 6.91 (2H, d, *J* = 8.9 Hz, H-2, 6), 6.58 (2H, d, *J* = 8.9 Hz, H-3, 5), 6.69 (1H, *J* = 12.2 Hz, H-6'a), 4.74 (1H, d, *J* = 7.4 Hz, H-1'), 4.38 (1H, d, *J* = 12.1 Hz, H-6'b), 3.86 (6H, s, 3''-OCH₃ and 5''-OCH₃), 3.39-3.72 (4H, m, H-2'-5''); ¹³C-NMR (125 MHz, MeOH-*d*₄): δ 168.0 (C-7''), 154.0 (C-4), 152.4 (C-1), 149.1 (C-3'', 5''), 142.5 (C-4''), 125.4 (C-1''), 119.6 (C-2, 6), 116.7 (C-3, 5), 108.5

(C-2'', 6''), 103.8 (C-1'), 78.0 (C-3'), 75.7 (C-5'), 75.1 (C-2'), 72.2 (C-4'), 65.4 (C-6'), 57.1 (3''-OCH₃ and 5''-OCH₃)

Breynioside A (18): Brown amorphous solid; ESI-Q-TOF-MS m/z 391.1043 [M – H][–] (calcd. for C₁₉H₂₀O₉, 391.1029); ¹H-NMR (500 MHz, MeOH-*d*₄): δ 7.90 (2H, d, *J* = 8.7 Hz, H-2', 6'), 6.94 (2H, d, *J* = 8.9 Hz, H-2, 6), 6.86 (2H, d, *J* = 8.7 Hz, H-3', 5'), 6.60 (2H, d, *J* = 8.9 Hz, H-3, 5), 3.41–3.87 (6H, m, H-2'-6'); ¹³C-NMR (125 MHz, MeOH-*d*₄): δ 168.0 (C-7''), 163.8 (C-4''), 154.0 (C-4), 152.4 (C-1), 133.0 (C-6''), 133.0 (C-2''), 122.3 (C-1''), 119.7 (C-6), 119.7 (C-2), 116.7 (C-3, 5), 116.4 (C-5''), 116.4 (C-3''), 103.8 (C-1'), 78.1 (C-3'), 75.7 (C-5'), 75.1 (C-2'), 72.2 (C-4'), 65.2 (C-6').

Phenylethyl-rutinoside (19): White amorphous powder; ESI-Q-TOF-MS: m/z 453.1748 [M + Na]⁺ (calcd. for C₂₀H₃₀O₁₀Na, 453.1737); ¹H-NMR (500 MHz, MeOH-*d*₄): δ 7.27 (2H, m, H-2, 6), 7.26 (2H, o, H-3, 5), 7.17 (1H, o, H-4), 4.74 (1H, d, *J* = 1.3 Hz, H-1''), 4.29 (1H, d, *J* = 7.8 Hz, H-1'), 4.04 (1H, m, H-8a), 3.77 (1H, m, H-8b), 2.94 (2H, td, *J* = 7.3, 3.0 Hz, H-7), 1.25 (1H, d, *J* = 6.2 Hz, H-6''); ¹³C-NMR (125 MHz, MeOH-*d*₄): δ 140.1 (C-1), 130.1 (C-3, 5), 129.5 (C-2, 6), 127.3 (C-4), 104.7 (C-1'), 102.4 (C-1''), 78.3 (C-3'), 77.1 (C-5'), 75.3 (C-2'), 74.2 (C-4''), 72.5 (C-3''), 72.3 (C-2''), 71.9 (C-8), 71.8 (C-4'), 69.9 (C-5''), 68.4 (C-6'), 37.4 (C-7), 18.5 (C-6'').

Icariside D1 (20): White powder; ESI-Q-TOF-MS: m/z 439.1581 [M + Na]⁺ (calcd. for C₁₉H₂₈O₁₀Na, 439.1580); ¹H-NMR (500 MHz, pyridine-*d*₅): δ 7.29 (2H, o, H-2, 6), 7.27 (2H, o, H-3, 5), 7.17 (1H, o, H-4), 5.82 (1H, d, *J* = 2.5 Hz, H-1''), 4.85 (1H, d, *J* = 7.8 Hz, H-1'), 4.35 (1H, m, H-8a), 3.91 (1H, m, H-8b), 3.00 (2H, t, *J* = 7.3 Hz, H-7); ¹³C-NMR (125 MHz, pyridine-*d*₅): δ 139.7 (C-1), 129.8 (C-3, 5), 129.8 (C-5), 129.0 (C-2, 6), 126.7 (C-4), 111.5 (C-1''), 105.0 (C-1'), 80.8 (C-3''), 78.9 (C-3'), 78.1 (C-2''), 77.5 (C-5'), 75.4 (C-2'), 75.4 (C-4''), 70.9 (C-8, 4'), 69.3 (C-6'), 65.9 (C-5''), 37.0 (C-7).

Hexenyl-rutinoside (21): White amorphous powder; ESI-Q-TOF-MS: m/z 431.1892 [M + Na]⁺ (calcd. for C₁₈H₃₂O₁₀Na, 431.1893); ¹H-NMR (500 MHz, MeOH-*d*₄): δ 5.46 (1H, o, H-4), 5.40 (1H, o, H-3), 4.74 (1H, d, *J* = 1.3 Hz, H-1''), 4.25 (1H, d, *J* = 7.8 Hz, H-1'), 3.81 (1H, m, H-1a), 3.54 (1H, m, H-1b), 2.38 (2H, m, H-2), 2.08 (2H, m, H-5), 1.26 (3H, d, *J* = 6.3 Hz, H-6''); ¹³C-NMR (125 MHz, MeOH-*d*₄): δ 134.7 (C-4), 126.1 (C-3), 104.6 (C-1'), 102.4 (C-1''), 78.2 (C-3'), 77.0 (C-5'), 75.2 (C-2'), 74.2 (C-4''), 72.5 (C-3''), 72.4 (C-2''), 71.8 (C-4'), 70.7 (C-1), 69.9 (C-5''), 68.3 (C-6'), 28.9 (C-2), 21.6 (C-5), 18.1 (C-6''), 14.7 (C-6).

Everlastoside C (22): Black powder; ESI-Q-TOF-MS: m/z 405.1741 [M + Na]⁺ (calcd. for C₁₆H₃₀O₁₀Na, 405.1737); ¹H-NMR (500 MHz, pyridine-*d*₅): δ 5.83 (1H, d, *J* = 2.3 Hz, H-1''), 4.81 (1H, d, *J* = 7.8 Hz, H-1'), 4.19 (1H, m, H-1a), 3.68 (1H, m, H-1b), 1.72 (1H, m, H-3), 1.52 (2H, dd, *J* = 13.4, 6.7 Hz, H-2), 0.82 (3H, d, *J* = 5.4 Hz, H-4), 0.80 (3H, d, *J* = 5.4 Hz, H-5); ¹³C-NMR (125 MHz, pyridine-*d*₅): δ 111.5 (C-1''), 105.0 (C-1'), 80.8 (C-3''), 78.9 (C-3'), 78.1 (C-2''), 77.5 (C-5'), 75.4 (C-2'), 75.4 (C-4''), 70.9 (C-4'), 69.3 (C-6'), 68.5 (C-1), 65.9 (C-5''), 39.3 (C-2), 25.4 (C-3), 23.0 (C-5), 22.9 (C-4).

Berganin (23): Brown powder; ESI-Q-TOF-MS: m/z 351.0701 [M + Na]⁺ (calcd. for C₁₄H₁₆O₉Na, 351.0692); ¹H-NMR (500 MHz, DMSO-*d*₆): δ 7.01 (1H, s, H-7), 4.98 (1H, d, *J* = 10.8 Hz, H-10b), 3.99 (1H, dd, *J* = 10.8, 9.6 Hz, H-4a), 3.85 (1H, brd, *J* = 11.4 Hz, H-11a), 3.78 (1H, s, OMe), 3.64 (1H, brd, *J* = 10.3 Hz, H-4), 3.58 (1H, m, H-2), 3.44 (1H, o, H-11b), 3.19 (1H, t, *J* = 8.7 Hz, H-3); ¹³C-NMR (125 MHz, DMSO-*d*₆): δ 163.8 (C-6), 151.4 (C-8), 148.5 (C-10), 141.0 (C-9), 118.5 (C-6a), 116.3 (C-10a), 109.9 (C-7), 82.2 (C-2), 80.2 (C-4a), 74.1 (C-4), 72.5 (C-10b), 71.1 (C-3), 61.5 (C-11).

Citroside A (24): Brown amorphous powder; ESI-Q-TOF-MS: m/z 409.1842 [M + Na]⁺ (calcd. for C₁₉H₃₀O₈Na, 409.1838); ¹H-NMR (500 MHz, MeOH-*d*₄): δ 5.89 (1H, s, H-8), 4.52 (1H, d, *J* = 7.7 Hz, H-1'), 4.32 (1H, m, H-3), 2.48 (1H, ddd, *J* = 13.4, 4.0, 2.1 Hz, H-4a), 2.19 (3H, s, H-11), 1.92 (1H, d, *J* = 1.4 Hz, H-2a), 1.47 (3H, s, H-10), 1.38 (3H, s, H-12), 1.36 (3H, d, *J* = 2.3 Hz, H-4b), 1.34 (3H, d, *J* = 1.5 Hz, H-2b), 1.15 (3H, s, H-13); ¹³C-NMR (125 MHz, MeOH-*d*₄): δ 213.1 (C-9), 200.8 (C-7), 119.2 (C-6), 101.5 (C-8), 98.8 (C-1'), 78.8 (C-5), 78.7 (C-3'), 77.9 (C-5'), 75.4 (C-2'), 71.8 (C-4'), 63.9 (C-3), 63.0 (C-6'), 50.0 (C-2), 48.2 (C-4), 37.1 (C-1), 32.6 (C-13), 30.2 (C-12), 26.8 (C-11), 26.7 (C-10).

3. Materials and Methods

3.1. General Experiments

$^1\text{H-NMR}$ (500 MHz) and $^{13}\text{C-NMR}$ (125MHz) data were obtained using a Bruker Avance III 500 Spectrometer (Bruker, Karlsruhe, Germany). ESI-Q-TOF-MS spectra were acquired using an Agilent 6530 Accurate-Mass Q-TOF LC/MS system (Agilent Technologies, Santa Clara, CA, USA). Preparative-scale high performance liquid chromatography (HPLC) was performed using a Gilson HPLC system (Middleton, WI, USA) composed of a binary pump, a liquid handler, and a UV/VIS detector. Gas chromatography (GC) was performed using a GC353B-FSL (GL Sciences Inc., Tokyo, Japan) and a flame ionization detector. A Jasco P-2000 polarimeter and a J-815 CD spectrometer (Jasco, Tokyo, Japan) were used to record optical rotation and circular dichroism (CD) spectra, respectively. UV absorbance was recorded using a UV-1800 spectrophotometer (Shimadzu, Kyoto, Japan). Silica gel (40–63 μm , Merck, Germany), ODS resin (S-5 μm , YMC Co., Tokyo, Japan), and SephadexTM LH-20 (GE Healthcare, Chicago, IL, USA) were used in liquid column chromatography, and thin layer chromatography was performed using Silicagel 60 F254 (Merck, Darmstadt, Germany). The preparative HPLC column was a Luna C18 (21.2 \times 250 mm I.D., 5 μm ; Phenomenex, Torrance, CA, USA). A BPX50 column (0.25 mm \times 30 m; Trajan Scientific and Medical, Victoria, Australia) was used to perform GC analysis. Authentic D-glucose was purchased from Sigma-Aldrich Korea (Yongin, Korea). Organic solvents used in extraction, partition, and column chromatography were of analytical grade and were purchased from Dae-Jung Chemical Co. Ltd. (Seoul, Korea). Methanol and acetonitrile for HPLC were provided by Thermo Fisher Scientific Korea (Seoul, Korea).

3.2. Plant Material

The aerial parts of *Leea asiatica* were collected from Popa Mountain National Park (Mandalay, Myanmar) in August 2011. Khin Myo Htwe (Popa Mountain National Park) identified specimens of *L. asiatica* and a voucher specimen (#PopaLeeaA082011) was deposited at the Herbarium of the College of Pharmacy, the Catholic University of Korea.

3.3. Extraction and Isolation

The dried *L. asiatica* (651.4 g) samples were treated with methanol and extracts were obtained through immersion in an ultrasonic bath (3 h \times 3 times). This process yielded methanol-soluble extracts (35.3 g). The methanol-soluble extracts were suspended in water and partitioned sequentially with organic solvents to yield *n*-hexane- (11.2 g), ethyl acetate- (9.1 g), and *n*-butanol-soluble extracts (6.1 g). The detailed isolation schemes for compounds 1–24 from organic solvent soluble extracts are described in Supplementary Information SI 9.

3.4. Acid Hydrolysis of Compound 1

Acid hydrolysis of compound 1 was carried out based on the previous report [47]. Derivatized authentic D-glucose gave GC peaks at t_R 11.84 min and the t_R of hydrolysate of 1 was similar to that of authentic D-glucose.

Supplementary Materials: 1-, 2-dimensional NMR, ESI-Q-TOF-MS, CD, and UV spectroscopic data of 1 are available online.

Author Contributions: K.D.Y. designed and supervised the research. R.T. and H.W.K. performed the experiment and analyzed spectroscopic data. All authors wrote, reviewed, and approved the final version of manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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Sample Availability: Samples of the compounds **1**, **2**, **4**, **6**, **9**, **10**, **12** and **17** are stored in DMSO and available from the authors.



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