SUPPORTING INFORMATION

Pomegranate's Neuroprotective Effects against Alzheimer's Disease are Mediated by Urolithins, its Ellagitannin-Gut Microbial Derived Metabolites

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List of Supporting Information

General Experimental Procedures. All Nuclear Magnetic Resonance experiments were acquired on a Varian 500 MHz instrument. Unless otherwise stated, deuterated methanol (CD_3OD) was used as solvent. For compound identification, all high resolution electrospray ionization mass spectral (HRESIMS) data were acquired on a Synapt G2-S QTOF mass spectrometer (Waters, Milford, MA, USA). Analytical and semi-preparative high performance liquid chromatography (HPLC) were performed on a Hitachi Elite LaChrom system consisting of a L2130 pump, L-2200 autosampler, and a L-2455 Diode Array Detector all operated by EZChrom Elite software. Medium-pressure liquid chromatography (MPLC) was carried out on prepacked C18 columns connected to a DLC-10/11 isocratic liquid chromatography pump (D-Star Instruments, Manassas, VA, USA). For worm-uptake studies, all mass spectral information were acquired on a Shimadzu UFLC system (3 LC-20AD pumps, Degasser DGU-$20A_{5R}$, autosampler SIL-20AC HT, column oven CTO-20AC, Analyst v.1.6.2 software; Shimadzu, Kyoto, Japan) coupled to an ABSCIEX QTrap 4500 mass spectrometer (Concord, Ontario, Canada). All solvents were obtained from Sigma-Aldrich (St. Louis, MO, USA).

Isolation and Identification of Compounds from the Pomegranate Extract (PE). The PE (3.8 g) was dissolved in methanol and subjected to a Sephadex LH-20 column (4.5 x 90 cm), eluting with a gradient solvent system of MeOH:H_2O (30:70, 50:50, 70:30, and 100:0; v/v , each 500 mL) to afford seven fractions: A-G. Fraction B (53.8 mg) was purified by semi-preparative HPLC by eluting with a gradient solvent system of MeOH:H_2O (0-20 min: 25:75 to 50:50; 20-21 min: 50:50 to 100:0; 21-22 min: 100:0; 22-23 min: 100:0 to 25:75; 23-30 min: 25:75; v/v, 3 mL/min) to yield compounds **12** (4.5 mg) and **17** (5.8 mg). Fraction C (42.5 mg) was purified by

semi-preparative HPLC with a gradient solvent system of MeOH:H_2O (0-20 min: 10:90 to 35:65; 20-21 min: 35:65 to 100:0; 21-22 min: 100:0; 22-23 min: 100:0 to 10:90; 23-30 min: 10:90; v/v, 3 mL/min) to yield compounds **2** (5.3 mg), **3** (1.5 mg) and gallic acid (2.7 mg). Purification of fraction D with semi-preparative HPLC by eluting with a gradient solvent system of MeOH-H_2O (0-20 min: 25:75 to 60:40; 20-21 min: 60:40 to 100:0; 21-22 min: 100:0; 22-23 min: 100:0 to 25:75; 23-30 min: 25:75; v/v, 3 mL/min) afforded compounds **13** (2.0 mg) and **14** (1.5 mg). Fraction E was subjected to C18 MPLC, by eluting with a gradient solvent system of MeOH:H_2O (0:100, 5:95, 10:90, 20:80, and 100:0; v/v, each 500 mL) to afford five sub-fractions: E1–E5. Purification of sub-fraction E1 by semi-preparative HPLC, eluting with a gradient solvent system of MeOH-H_2O (0-20 min: 5:95 to 15:85; 20-21 min: 15:85 to 100:0; 21-22 min: 100:0 to 5:95; 22-29 min: 5:95; v/v, 3 mL/min), yielded compounds **4** (3.0 mg) and **11** (3.2 mg). Sub-fraction E2 was purified by semi-preparative HPLC, eluting with a gradient solvent system of MeOH:H_2O (0-20 min: 10:90 to 22:78; 20-21 min: 22:78 to 100:0; 21-22 min: 100:0 to 10:90; 22-29 min: 10:90; v/v, 3 mL/min) to yield compounds **5** (5.5 mg) and **16** (6.0 mg). Purification of sub-fraction E3 by semi-preparative HPLC eluting with an isocratic solvent system of MeOH:H_2O (17:83, v/v) yielded compound **1** (7.5 mg). Sub-fraction E4 was purified by semi-preparative HPLC by eluting with a gradient solvent system of MeOH:H_2O (0-30 min: 20:80 to 40:60; 30-31 min: 40:60 to 100:0; 31-32 min: 100:0 to 20:80; 32-39 min: 20:80; v/v, 3 mL/min) to yield compounds **8** (3.5 mg), **9** (2.0 mg) and **10** (8.7 mg). Purification of sub-fraction E5 with semi-preparative HPLC, eluting with a gradient solvent system of MeOH:H_2O (0-20 min: 30:70 to 55:45; 20-21 min: 55:45 to 100:0; 21-22 min: 100:0 to 30:70; 22-29 min: 30:70; v/v, 3 mL/min) yielded compounds **15** (3.1 mg) and ellagic acid (4.7 mg). Fraction G was subjected to C18 MPLC, eluting with a gradient solvent system of MeOH:H_2O (0:100 to 100:0;

v/v) to afford four sub-fractions: G1–G4. Sub-fraction G1 was purified by semi-preparative HPLC, eluted with a gradient solvent system of MeOH:H_2O (0-25 min: 10:90 to 17:83; 25-26 min: 17:83 to 100:0; 26-27 min: 100:0 to 10:90; 27-35 min: 10:90; v/v, 3 mL/min) yielded compounds **7** (3.2 mg), punicalin (4.8 mg) and punicalagin (12.1 mg). Purification of sub-fraction G4 by semi-preparative HPLC, eluted with a gradient solvent system of MeOH:H_2O (0-35 min: 20:80 to 50:50; 35-36 min: 50:50 to 100:0; 36-37 min: 100:0 to 20:80; 37-45 min: 20:80; v/v, 3 mL/min), yielded compound **6** (9.5 mg).

Identification of Compounds in the PE. A total of twenty one compounds (**1-21**) (chemical structures shown in **Figure 1B**) were identified in the PE. The compounds included a new compound, assigned the common name of pomellatannin (**1**), whose structure was elucidated based on extensive analysis of 1D and 2D NMR and HRMS data (further described below). The structures of sixteen known compounds (**2-17**) were identified based on ^{1}H and/or ^{13}C NMR data and by comparison of these data to published literature reports. Also, four constituents commonly known to be found in pomegranate, namely, punicalagin (PA), punicalin, ellagic acid (EA), and gallic acid (GA), were identified by comparing their retention times and UV spectra, based on HPLC-DAD methods with those of authentic chemical standards (purchased from Sigma).

Pomellatannin (**1**), Light yellowish amorphous powder; HRESIMS *m*/*z* 839.1196 $[M-H]^-$, calcd. for molecular formula $C_{37}H_{28}O_{23}$; ^{1}H-NMR (CD_3OD, 500 MHz) Glucose: δ 6.10 (1H, brs, H-1), 4.91 (1H, brs, H-2), 4.56 (1H, brs, H-3), 5.17 (1H, brs, H-4), 4.58 (1H, dd, *J* = 7.4, 5.7 Hz, H-5), 5.10 (1H, dd, *J* = 11.6, 7.4 Hz, H-6), 4.03 (1H, dd, *J* = 11.6, 5.7 Hz, H-6); HHDP: δ 6.85 (1H, s,

H-3′), 6.74 (1H, s, H-3″); (*S*)-ADHHDP: δ 4.86 (1H, overlap in solvent, H-1‴), 6.30 (1H, s, H-3‴), 3.42 (1H, d, *J* = 15.8 Hz, H-8‴), 2.81 (1H, d, *J* = 15.8 Hz, H-8‴), 2.19 (3H, s, H-10‴), 7.17 (1H, s, H-3⁗); ^{13}C-NMR (CD_3OD, 125 MHz) Glucose: δ 89.6 (C-1), 70.1 (C-2), 59.8 (C-3), 68.3 (C-4), 70.6 (C-5), 63.5 (C-6); HHDP: δ 116.5 (C-1′), 123.8 (C-2′), 109.1 (C-3′), 144.0 (C-4′), 136.9 (C-5′), 143.7 (C-6′), 166.3 (C-7′), 115.1 (C-1″), 124.2 (C-2″), 107.3 (C-3″), 144.4 (C-4″), 136.0 (C-5″), 143.6 (C-6″), 168.8 (C-7″); (*S*)-ADHHDP: δ 50.8 (C-1‴), 144.8 (C-2‴), 126.5 (C-3‴), 197.4 (C-4‴), 80.2 (C-5‴), 108.3 (C-6‴), 164.4 (C-7‴), 49.0 (C-8‴), 206.8 (C-9‴), 30.7 (C-10‴), 118.0 (C-1⁗), 118.5 (C-2⁗), 112.5 (C-3⁗), 146.6 (C-4⁗), 136.0 (C-5⁗), 145.9 (C-6⁗), 165.1 (C-7⁗).

Punigluconin (**2**), Light yellowish amorphous powder; ^{1}H-NMR (CD_3OD, 500 MHz) Sugar: δ 5.26 (1H, d, *J* = 4.2 Hz, H-2), 4.42 (1H, dd, *J* = 7.9, 4.2 Hz, H-3), 5.50 (1H, brd, *J* = 7.9 Hz, H-4), 5.69 (1H, m, H-5), 4.82 (1H, dd, *J* = 12.2, 1.9 Hz, H-6), 4.01 (1H, dd, *J* = 12.2, 3.3 Hz, H-6); HHDP: δ 6.83 (1H, s), 6.48 (1H, s); Galloyl: δ 7.06 (2H, s), 7.02 (2H, s); ^{13}C-NMR (CD_3OD, 125 MHz) Sugar: δ 170.1 (C-1), 73.0 (C-2), 69.9 (C-3), 71.9 (C-4), 70.6 (C-5), 64.0 (C-6); HHDP: δ 169.1, 167.4, 144.5, 144.4, 143.6, 143.4, 136.4, 135.5, 125.6, 124.3, 115.4, 114.4, 108.1, 106.2; 2-Galloyl: δ 165.9, 144.8 (2C), 138.7, 119.2, 109.3(2C); 5-Galloyl: δ 165.8, 145.0 (2C), 138.7, 119.3, 108.9 (2C). ^{1}H and ^{13}C NMR data were consistent with literature.

6-O-Galloyl-D-glucose (**3**), White amorphous powder; ^{1}H-NMR (CD_3OD, 500 MHz) Glucose: δ 5.12 (1H, d, *J* = 3.5 Hz, H-1*α*), 4.52 (1H, d, *J* = 7.8 Hz, H-1*β*), 3.40 (1H, m, H-2*α*), 3.19 (1H, t, *J* = 9.1, 7.8 Hz, H-2*β*), 3.44 (2H, m, H-3*α*, 4*α*), 3.39 (1H, m, H-3*β*), 3.73 (1H, m, H-4*β*), 3.59 (1H, m, H-5*β*), 4.37–4.57 (4H, m, H_2-6*α*, H_2-6*β*); Galloyl: 7.10 (2H, s); ^{13}C-NMR (CD_3OD, 125 MHz) Glucose: δ 96.6 (C-1*β*), 92.5 (C-1*α*), 72.4 (C-2*α*), 74.8 (C-2*β*), 70.5 (C-3*α*), 76.5 (C-3*β*),

70.3 (C-4*α*), 73.4 (C-4*β*), 69.5 (C-5*α*), 74.2 (C-5*β*), 63.5 (C-6*α*, 6*β*); Galloyl: 108.7 (2C), 120.0, 138.4, 145.1 (2C), 167.0. ^{1}H and ^{13}C NMR data were consistent with literature.

Gemin D (**4**), Light yellowish amorphous powder; ^{1}H-NMR (CD_3OD, 500 MHz) Glucose: δ 5.21 (1H, d, *J* = 3.2 Hz, H-1*α*), 4.66 (1H, d, *J* = 7.5 Hz, H-1*β*), 3.79 (1H, m, H-2*α*), 3.52 (1H, t, *J* = 9.0, 7.5 Hz, H-2*β*), 5.51 (1H, m, H-3*α*), 5.31 (1H, m, H-3*β*), 4.97 (1H, m, H-4*α*), 5.00 (1H, t, *J* = 9.0 Hz, H-4*β*), 4.56 (1H, m, H-5*α*), 4.06 (1H, m, H-5*β*), 5.24–5.33 (2H, m, H-6*α*, H-6*β*), 3.79–3.86 (2H, m, H-6*α*, H-6*β*); HHDP: δ 6.57 (1H, s), 6.45 (1H, s); Galloyl: 6.99 (2H, s); ^{13}C-NMR (CD_3OD, 125 MHz) Glucose: δ 97.7 (C-1*β*), 93.0 (C-1*α*), 71.0 (C-2*α*), 73.6 (C-2*β*), 73.4 (C-3*α*), 74.9 (C-3*β*), 70.7 (C-4*α*), 70.5 (C-4*β*), 66.3 (C-5*α*), 71.2 (C-5*β*), 62.9, 63.0 (C-6*α*, 6*β*); HHDP: 168.4 (168.3), 168.1 (168.0), 144.5, 144.4, 143.3 (2C), 136.14, 136.08, 125.0 (124.9), 124.65 (124.58), 115.3, 114.9, 107.1, 106.8; Galloyl: 109.1 (2C), 119.79 (119.94), 138.27 (138.33), 144.78 (144.80) (2C), 166.7 (166.9). ^{1}H and ^{13}C NMR data were consistent with literature.

Hippomanin A (**5**), Light yellowish amorphous powder; ^{1}H-NMR (CD_3OD, 500 MHz) Glucose: δ 5.39 (1H, d, *J* = 3.7 Hz, H-1*α*), 4.78 (1H, d, *J* = 8.4 Hz, H-1*β*), 4.85 (1H, m, H-2*α*), 4.97 (1H, t, *J* = 8.4, 9.1 Hz, H-2*β*), 4.15 (1H, t, *J* = 9.8 Hz, H-3*α*), 3.87 (1H, t, *J* = 9.1 Hz, H-3*β*), 4.87 (1H, m, H-4*α*), 4.91 (1H, t, *J* = 9.8 Hz, H-4*β*), 4.45 (1H, m, H-5*α*), 3.97 (1H, m, H-5*β*), 5.18–5.26 (2H, m, H-6*α*, H-6*β*), 3.75–3.89 (2H, m, H-6*α*, H-6*β*); HHDP: δ 6.69 (6.66) (1H, s), 6.58 (6.57) (1H, s); Galloyl: 7.11 (7.09) (2H, s); ^{13}C-NMR (CD_3OD, 125 MHz) Glucose: δ 95.8 (C-1*β*), 90.2 (C-1*α*), 74.3 (C-2*α*), 75.7 (C-2*β*), 69.7 (C-3*α*), 72.9 (C-3*β*), 72.6 (C-4*α*), 72.1 (C-4*β*), 66.3 (C-5*α*), 71.5 (C-5*β*), 63.1, 63.2 (C-6*α*, 6*β*); HHDP: 168.6 (168.5), 168.2 (168.1), 144.5, 144.4, 143.4, 143.3, 136.14, 135.9, 125.1, 125.0, 115.3, 115.2, 107.1, 107.0; Galloyl: 109.0 (108.9)

(2C), 119.8 (120.1), 138.5 (138.4), 145.0 (2C), 166.5 (166.0). ^{1}H and ^{13}C NMR data were consistent with literature.

Praecoxin B (**6**), Light yellowish amorphous powder; ^{1}H-NMR (CD_3OD, 500 MHz) Glucose: δ 5.42 (1H, d, *J* = 3.7 Hz, H-1*α*), 5.07 (1H, d, *J* = 8.4 Hz, H-1*β*), 5.15 (1H, dd, *J* = 9.2, 3.7 Hz, H-2*α*), 4.92 (1H, t, *J* = 8.4, 9.1 Hz, H-2*β*), 5.65 (1H, t, *J* = 9.8 Hz, H-3*α*), 5.41 (1H, t, *J* = 9.1 Hz, H-3*β*), 5.58 (1H, t, *J* = 9.1 Hz, H-4*α*), 5.54 (1H, t, *J* = 9.8 Hz, H-4*β*), 4.48 (1H, m, H-5*α*), 4.14 (1H, m, H-5*β*), 4.44–4.50 (2H, m, H-6*α*, H-6*β*), 4.24–4.29 (2H, m, H-6*α*, H-6*β*); HHDP: δ 6.61 (6.59) (1H, s), 6.35 (6.36) (1H, s); Galloyl: 7.11 (7.10) (2H, s), 7.07 (7.06) (2H, s); ^{13}C-NMR (CD_3OD, 125 MHz) Glucose: δ 94.0 (C-1*β*), 90.6 (C-1*α*), 74.5 (C-2*α*), 76.8 (C-2*β*), 74.7 (C-3*α*), 76.9 (C-3*β*), 67.8 (C-4*α*), 67.5 (C-4*β*), 67.4 (C-5*α*), 72.3 (C-5*β*), 62.2 (C-6*α*, 6*β*); HHDP: 169.2, 169.0 (168.9), 144.4 (144.5), 144.4, 143.4, 143.3, 136.1 (136.0), 135.8, 125.2, 125.0, 114.0, 113.6, 106.7, 106.2; 4-Galloyl: 109.0 (2C), 118.9 (118.8), 139.0, 145.2 (2C), 166.5; 6-Galloyl: 108.9 (2C), 119.8 (119.7), 138.5, 145.0 (2C), 166.7. ^{1}H and ^{13}C NMR data were consistent with literature.

Pedunculagin (**7**), Light yellowish amorphous powder; ^{1}H-NMR (CD_3OD, 500 MHz) Glucose: δ 5.36 (1H, d, *J* = 4.2 Hz, H-1*α*), 4.95 (1H, d, *J* = 7.9 Hz, H-1*β*), 5.10 (1H, dd, *J* = 9.6, 4.2 Hz, H-2*α*), 4.95 (1H, m, H-2*β*), 5.46 (1H, t, *J* = 9.7 Hz, H-3*α*), 5.36 (1H, t, *J* = 9.1 Hz, H-3*β*), 5.58 (1H, t, *J* = 9.1 Hz, H-4*α*), 5.54 (1H, t, *J* = 9.8 Hz, H-4*β*), 4.58 (1H, m, H-5*α*), 4.14 (1H, m, H-5*β*), 4.44–4.50 (2H, m, H-6*α*, H-6*β*), 4.24–4.29 (2H, m, H-6*α*, H-6*β*); HHDP: δ 6.61 (6.59) (1H, s), 6.35 (6.36) (1H, s), 6.60 (6.58) (1H, s), 6.52 (6.49) (1H, s); ^{13}C-NMR (CD_3OD, 125 MHz) Glucose: δ 94.6 (C-1*β*), 90.9 (C-1*α*), 74.5 (C-2*α*), 76.8 (C-2*β*), 74.7 (C-3*α*), 76.9 (C-3*β*), 67.8 (C-4*α*), 67.5 (C-4*β*), 67.4 (C-5*α*), 72.3 (C-5*β*), 62.2 (C-6*α*, 6*β*); HHDP: 169.2, 169.0 (168.9), 144.4 (144.5), 144.4, 143.4, 143.3, 136.1 (136.0), 135.8, 125.2, 125.0, 114.0, 113.6, 106.7, 106.2; 4-

Galloyl: 109.0 (2C), 118.9 (118.8), 139.0, 145.2 (2C), 166.5; 6-Galloyl: 108.9 (2C), 119.8 (119.7), 138.5, 145.0 (2C), 166.7. ^{1}H and ^{13}C NMR data were consistent with literature.

1,6-di-O-Ggalloyl-β-D-glucose (**8**), white amorphous powder; ^{1}H-NMR (CD_3OD, 500 MHz) Glucose: δ 5.66 (1H, d, *J* = 7.0 Hz, H-1), 3.49-3.51 (3H, m, H-2, 3, 4), 3.72 (1H, m, H-5), 4.54 (1H, dd, *J* = 12.0, 1.8 Hz, H-6a), 4.40 (1H, dd, *J* = 12.0, 5.1 Hz, H-6b); Galloyl: 7.13 (2H, s), 7.07 (2H, s); ^{13}C-NMR (CD_3OD, 125 MHz) Glucose: δ 94.5 (C-1), 72.7 (C-2), 76.5 (C-3), 69.7 (C-4), 75.0 (C-5), 63.0 (C-6); Galloyl: 166.9, 165.6, 145.1 (2C), 145.0 (2C), 139.0, 138.4, 119.9, 119.2, 109.2 (2C), 108.8 (2C). ^{1}H and ^{13}C NMR data were consistent with literature.

Gallic acid-3-O-β-D-(6′-O-galloyl)-glucopyranoside (**9**), white amorphous powder; ^{1}H-NMR (CD_3OD, 500 MHz) Glucose: δ 4.88 (1H, d, *J* = 7.3 Hz, H-1), 3.48-3.55 (3H, m, H-2, 3, 4), 3.78 (1H, m, H-5), 4.64 (1H, dd, *J* = 12.0, 1.5 Hz, H-6a), 4.36 (1H, dd, *J* = 12.0, 5.5 Hz, H-6b); Galloyl: 7.15 (2H, s), 7.45 (1H, d, *J* = 2.1 Hz), 7.27 (1H, d, *J* = 2.1 Hz). ^{1}H NMR data were consistent with literature.

Isocorilagin (**10**), Light yellowish amorphous powder; ^{1}H-NMR (CD_3OD, 500 MHz) Glucose: δ 6.36 (1H, d, *J* = 1.4 Hz, H-1), 3.97 (1H, brs, H-2), 4.80 (1H, brs, H-3), 4.46 (1H, d, *J* = 2.5 Hz, H-4), 4.51 (1H, m, H-5), 4.95 (1H, dd, *J* = 11.0, 10.8 Hz, H-6a), 4.15 (1H, dd, *J* = 11.0, 8.2 Hz, H-6b); ^{13}C-NMR (CD_3OD, 125 MHz) Glucose: δ 93.6 (C-1), 68.1 (C-2), 70.3 (C-3), 61.0 (C-4), 74.8 (C-5), 63.6 (C-6); HHDP: 168.7, 167.1, 144.6, 144.2, 143.9, 143.8, 136.7, 136.2, 124.05, 124.02, 115.8, 115.3, 108.7, 106.9; Galloyl: 165.2, 145.0 (2C), 139.0, 119.2, 109.5 (2C). ^{1}H and ^{13}C NMR data were consistent with literature.

Casuariin (**11**), Light yellowish amorphous powder; ^{1}H-NMR (CD_3OD, 500 MHz): δ 6.75, 6.51, 6.34 (each 1H, s, HHDP ArH), 5.52 (1H, d, *J* = 4.8 Hz, H-1), 4.68 (1H, dd, *J* = 4.8, 1.4 Hz, H-2), 5.48 (1H, brs, H-3), 5.08 (1H, dd, *J* = 8.7, 1.6 Hz, H-4), 4.05 (1H, dd, *J* = 8.7, 2.8 Hz, H-5), 4.76

(1H, dd, *J* = 12.4, 2.8 Hz, H-6a), 3.85 (1H, d, *J* = 12.4 Hz, H-6b); ^{13}C-NMR (CD_3OD, 125 MHz): δ 66.7 (C-1), 76.9 (C-2), 69.8 (C-3), 76.4 (C-4), 67.8 (C-5), 67.3 (C-6); HHDP: 169.9, 169.5, 168.2, 165.7, 145.5, 145.2, 144.5 (2C), 143.5, 143.4, 143.1, 143.0, 138.5, 136.2, 135.5, 134.3, 126.4, 126.0, 124.1, 118.8, 116.0, 115.1, 115.2, 115.1, 114.5, 107.7, 106.2, 103.7. ^{1}H and ^{13}C NMR data were consistent with literature.

Ellagic acid-4-O-β-D-glucopyranose (**12**), Light yellowish amorphous powder; ^{1}H-NMR (CD_3OD, 500 MHz): δ 7.83 (1H, s, ArH), 7.62 (1H, s, ArH), 5.15 (1H, d, *J* = 6.9 Hz, H-1), 3.44-3.98 (6H, m, Glc H-2–H-6). ^{1}H NMR data were consistent with literature.

3,3′-Di-O-methylellagic acid-4-O-β-D-glucopyranose (**13**), Light yellowish amorphous powder; ^{1}H-NMR (CD_3OD, 500 MHz): δ 7.93 (1H, s, ArH), 7.58 (1H, s, ArH), 5.14 (1H, d, *J* = 7.3 Hz, H-1), 3.44-3.60 (4H, m, H-2, 3, 4, 5), 3.90 (1H, dd, *J* = 12.1, 2.0 Hz, H-6a), 3.74 (1H, dd, *J* = 12.1, 5.2 Hz, H-6b), 4.18, 4.19 (each 3H, s, MeO). ^{1}H NMR data were consistent with literature.[9]

4-O-α-L-Rhamnopyranosyl-ellagic acid (**14**), Light yellowish amorphous powder; ^{1}H-NMR (CD_3OD, 500 MHz): δ 7.93 (1H, s, ArH), 7.56 (1H, s, ArH), 5.57 (1H, brs, H-1), 4.18 (1H, brs, H-2), 3.99 (1H, dd, *J* = 9.6, 3.0 Hz, H-3), 3.51 (1H, t, *J* = 9.6 Hz, H-4), 3.73 (1H, m, H-5), 1.26 (3H, d, *J* = 6.6 Hz, H-6). ^{1}H NMR data were consistent with literature.

4-O-α-L-Arabinofuranosyl-ellagic acid (**15**), Light yellowish amorphous powder; ^{1}H-NMR (DMSO-*d*$_6$, 500 MHz): δ 7.70 (1H, s, ArH), 7.47 (1H, s, ArH), 5.61 (1H, brs, H-1), 4.32 (1H, brs, H-2), 3.85 (1H, m, H-3), 3.95 (1H, m, H-4), 3.60 (1H, dd, *J* = 12.0, 3.2 Hz, H-5a), 3.46 (1H, dd, *J* = 12.0, 5.4 Hz, H-5b). ^{13}C-NMR (DMSO-*d*$_6$, 500 MHz): δ 108.1 (C-1), 81.9 (C-2), 77.0 (C-3), 86.4 (C-4), 61.4 (C-5). ^{1}H and ^{13}C NMR data were consistent with literature.

Gallocatechin (**16**), White amorphous powder; ^{1}H-NMR (CD_3OD, 500 MHz): δ 6.40 (2H, s, H-2′, 6′), 5.91 (1H, d, *J* = 1.8 Hz, H-6), 5.86 (1H, d, *J* = 1.8 Hz, H-8), 4.53 (1H, d, *J* = 7.0 Hz, H-2),

3.96 (1H, m, H-3), 2.81 (1H, dd, *J* = 16.1, 5.2 Hz, H-4a), 2.50 (1H, dd, *J* = 16.1, 7.9 Hz, H-4b). ^{1}H NMR data were consistent with literature.

Brevifolincarboxylic acid (**17**), Light yellowish amorphous powder; ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 7.29 (1H, s), 4.36 (1H, dd, *J* = 7.6, 2.0 Hz), 2.99 (1H, dd, *J* = 18.6, 7.6 Hz), 2.42 (1H, dd, *J* = 18.6, 2.0 Hz). ^{1}H NMR data were consistent with literature.

Structure Elucidation of Compound 1. The compound was obtained as a light yellow amorphous solid, displayed a molecular formula of $C_{37}H_{28}O_{23}$, as determined by HRESIMS at *m/z* 839.1196 $[M-H]^-$ (calcd for $C_{37}H_{27}O_{23}$, 839.0943) which calculated for 24 degrees of unsaturation. The ^{1}H and ^{13}C NMR spectra of **1** showed signals due to a highly acylated hexopyranosyl moiety and aromatic and carboxylic carbons, indicative of compound **1** being an ellagitannin. The ^{1}H NMR signals at δ 6.85, 6.74 (each 1H, s) and characteristic ^{13}C NMR signals in the aromatic region indicated the presence of a hexahydroxydiphenoyl (HHDP) moiety, which was attached to C-1 and C-6 of glucose by the HMBC correlations from H-1 to C-7′, and from H-6 to C-7″. The glucose is a $^{1}C_4$ conformation based on the small coupling constants of the protons of the glucopyranosyl unit. Except for the NMR signals of the HHDP and glucose moieties, the remaining NMR signals of **1** showed signals similar to those of a moiety of acetone condensate of dehydrohexahydroxydiphenyl (DHHDP). The ^{1}H NMR signals of the singlet methyl (δ 2.19, 3H, s) and methylene (δ 3.42 and 2.81, each d, *J* = 15.8 Hz) groups, along with the ^{13}C NMR signal of the carbonyl carbon (δ 206.8) supported the presence of an acetone condensate of DHHDP, which was connected to C-2 and C-4 of the glucose based on the HMBC correlations from H-2 to C-7‴, and from H-4 to C-7⁗. The structure of compound **1** was elucidated as depicted, and assigned the common name of pomellatannin. Notably, the

isolation of acetone condensates of dehydroellagitannins has previously been reported from aqueous acetone extracts of ellagitannin-rich plant extracts and thus, these compounds, including compound **1**, are considered as artifacts formed during the extraction process.

Figure S1. Fluorescence reading generated from ThT binding assay

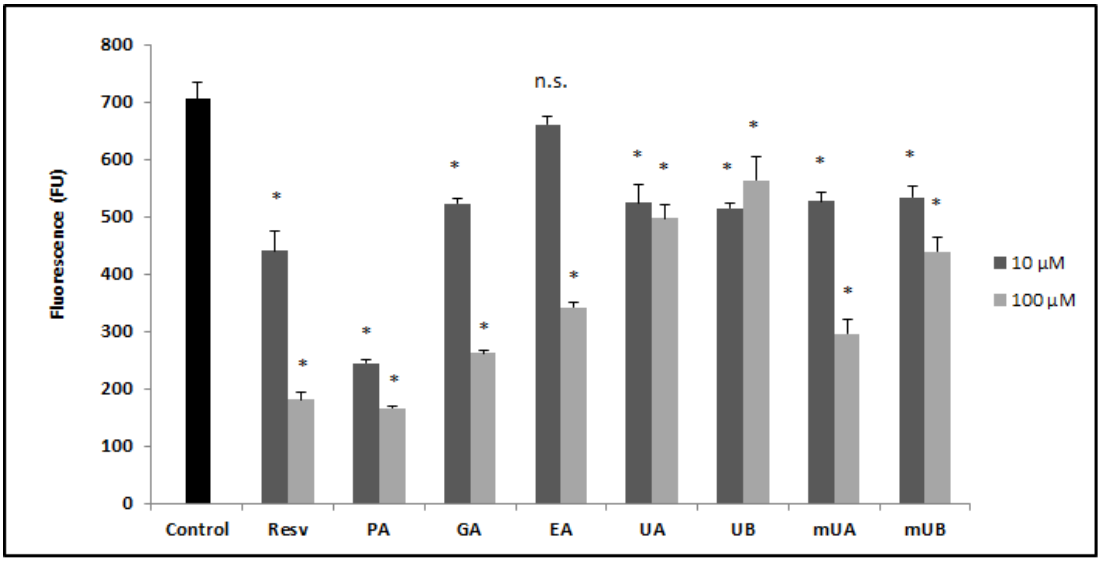

Figure S1. Fluorescence reading generated from ThT binding assay to measure the extent of Aß$_{1-42}$ fibrillation**.** Binding level of ThT is shown by mean fluorescence in arbitrary fluorescence unit (FU) ± S.D. (error bars). *p<0.05 vs control (Aβ$_{1-42}$ without any treatment), n=3. PE compounds (PA, GA) and urolithins (UA, UB, mUA and mUB) all significantly reduced ThT binding at both lower and higher concentrations of 10 and 100 µM while the EA treated group showed a significant decrease at the higher concentration of 100 µM. Resveratrol (Resv) at equivalent concentrations of 10 and 100 µM served as positive controls.

Liquid Chromatography Mass Spectroscopy (LC-MS/MS) Measurement of Urolithin Uptake by *C. elegans*. The uptake of urolithins in *C. elegans* (using UA as the model compound) was measured using a Shimadzu UFLC system (3 LC-20AD pumps, Degasser DGU-$20A_{5R}$, autosampler SIL-20AC HT, column oven CTO-20AC, Analyst v.1.6.2 software; Shimadzu, Kyoto, Japan) coupled to an ABSCIEX QTrap 4500 mass spectrometer (Concord, Ontario, Canada) using an electrospray source interface. Identification and separation were achieved on a reverse phase Phenomenex (Torrance, CA, USA) C18 column (250 x 4.6 mm, 5 μm) operating at 40 °C. The mobile phases were water:formic acid (99.9:0.1 v/v; solvent A) and methanol:formic acid (99.9:0.1 v/v; solvent B). The gradient solvent system was as follows: 0–20 min, 50-100% B; 20–25 min, 100% B; 25–27 min, 100–50% B, 27– 32 min, 50% B. The retention time of UA was 12 minutes and using this standard, we optimized the MS/MS fragmentation of UA over each of the specific 5 transitions as follows: [M+H] 229-195, 229-157, 229-139, 229-128, 229-114.9 (**Figure S2**). Each of the transitions is represented by a specific color: 195 blue, 157 red, 139 green, 128 grey, 114.9 pale blue. The untreated worm sample is shown in **Figure S3** and the UA-treated worm sample is shown in **Figure S4**.

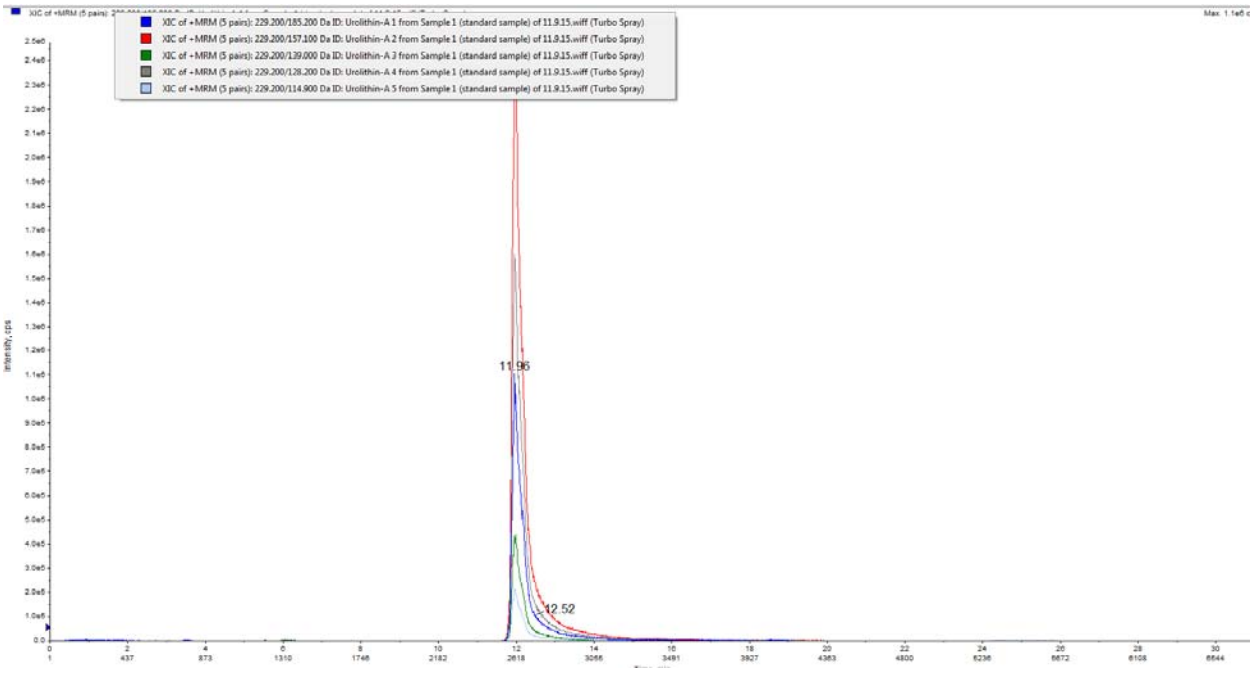

Figure S2. MS/MS transitions of the fragmentation of UA standard. Each transition is represented by a specific color: [M+H] 229-195 blue, 229-157 red, 229-139 green, 229-128 grey, 229-114.9 pale blue.

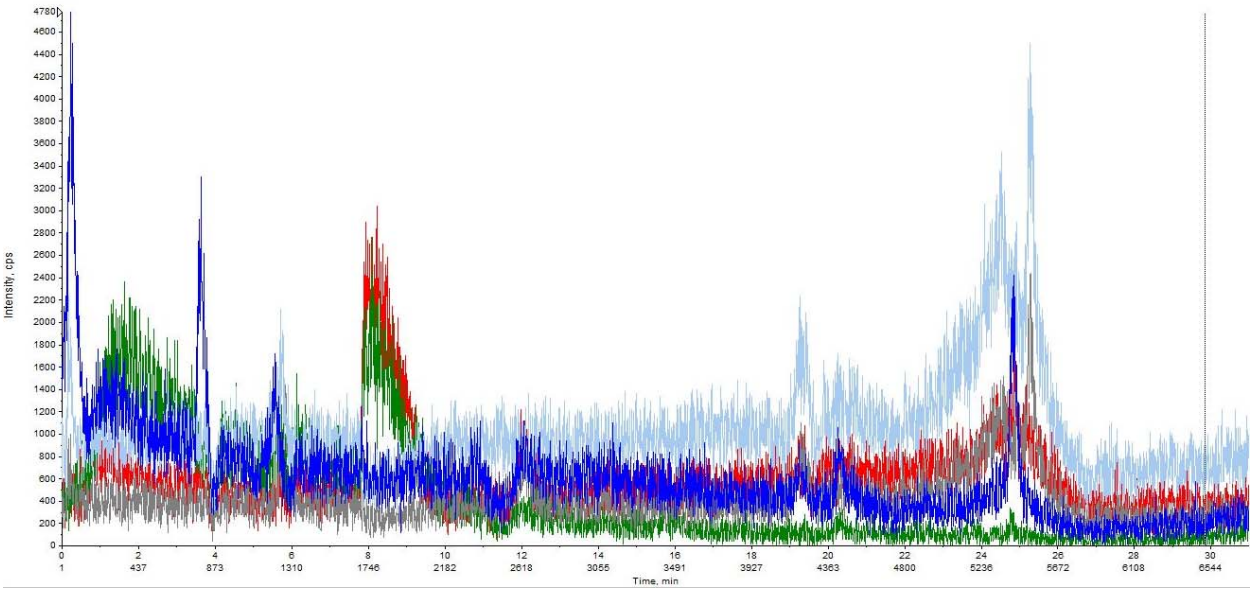

Figure S3. MS/MS transitions of the fragmentation of untreated worms. Each MS/MS transition of UA is represented by a specific color: [M+H] 229-195 blue, 229-157 red, 229-139 green, 229-128 grey, 229-114.9 pale blue.

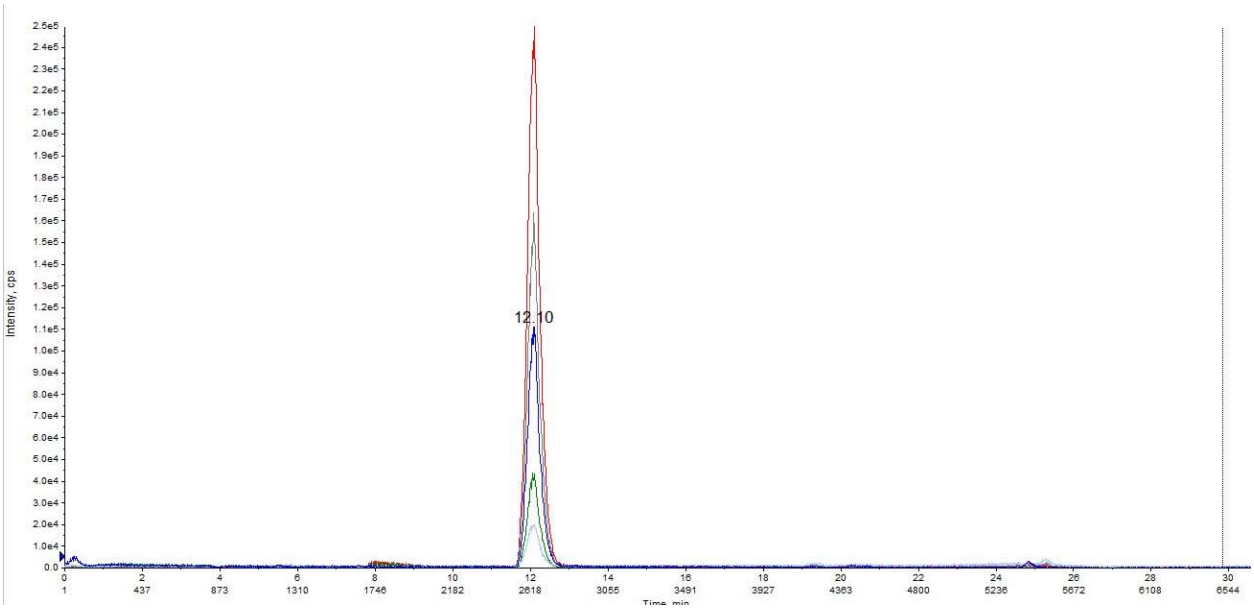

Figure S4. MS/MS transitions of the fragmentation of worms treated with UA. Each MS/MS transition of UA is represented by a specific color: [M+H] 229-195 blue, 229-157 red, 229-139 green, 229-128 grey, 229-114.9 pale blue.