Supporting Information for

# Resveratrol Sustains Insulin-degrading Enzyme Activity towards Aβ42

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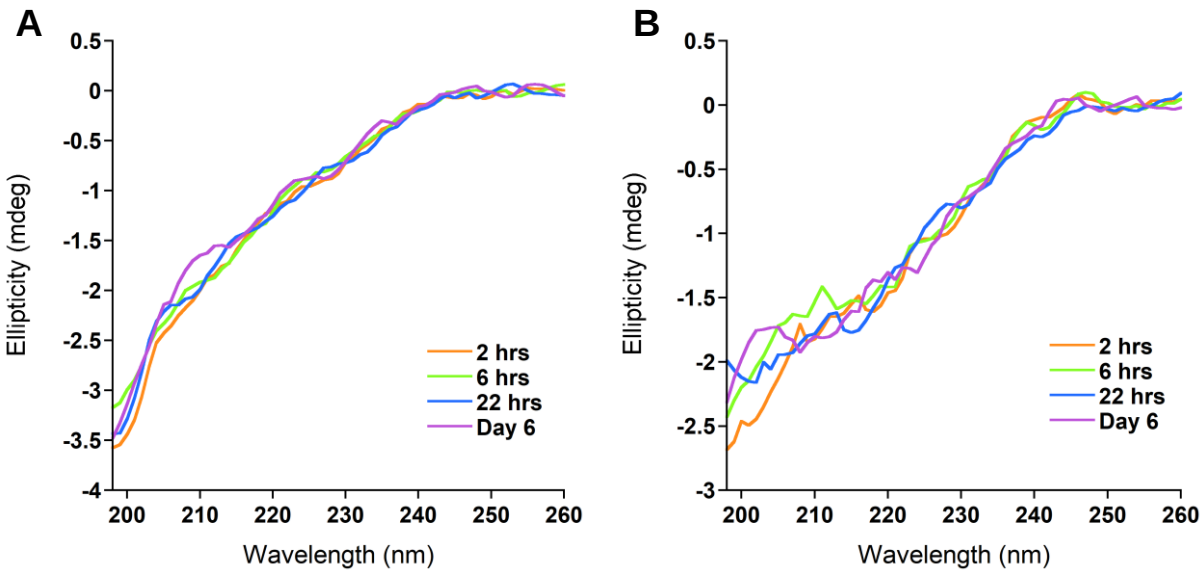


**Figure S1.** Aβ42 in the absence or presence of resveratrol at 4 °C is unstructured. Circular dichroic spectra of Aβ42 (25 μM in 10 mM phosphate buffer, pH 7.4) in the absence (A) and presence (B) of resveratrol (40 μM) recorded after 2 hours, 6 hours, 22 hours and 6 days of preparation show minima below 200 nm, indicating the presence of random coil.

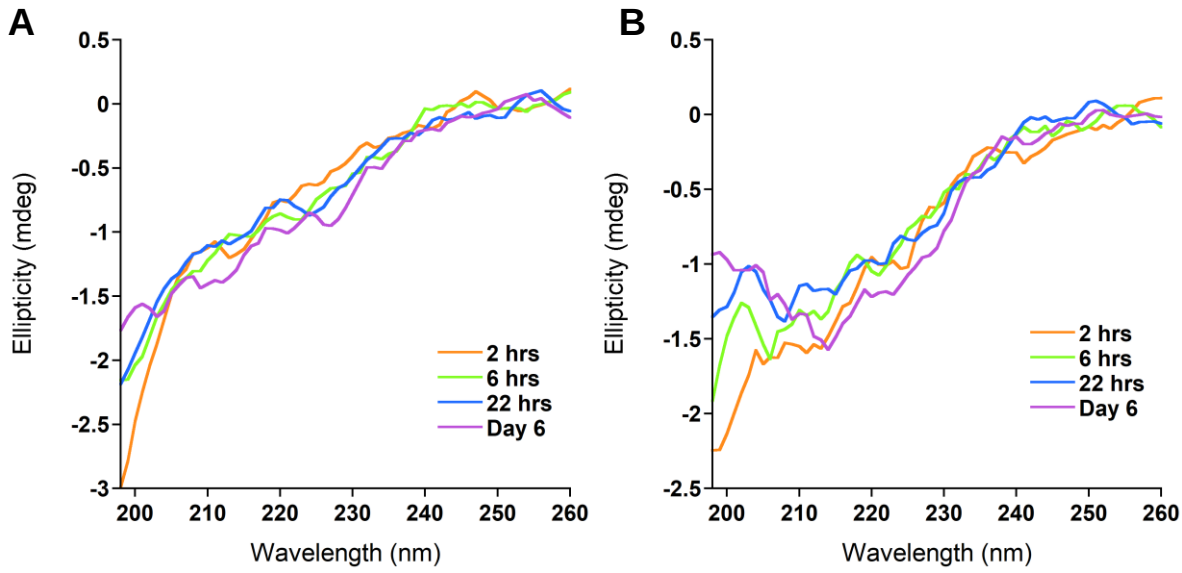


**Figure S2.** Digests of Aβ42 in the absence or presence of resveratrol at 4 °C contain unstructured peptides. Circular dichroic spectra of digests of Aβ42 (25 μM Aβ42 and 0.25 μM IDE (substrate-to-enzyme molar ratio of 100:1) in 10 mM phosphate buffer, pH 7.4) in the absence (A) and presence (B) of resveratrol (40 μM) recorded after 2 hours, 6 hours, 22 hours and 6 days of preparation show minima below 200 nm, indicating the presence of random coil.

**Table S1.** Secondary fragments resulting from IDE-dependent degradation of Aβ42 (25 μM in 10 mM phosphate buffer, pH 7.4) for 2 hours at 4 °C and substrate-to-enzyme molar ratio of 100:1.

| Fragments | Observed m/z | Charge | Observed Mass | Theoretical Mass | δ (Da)[1] |
|---|---|---|---|---|---|
| D1-H13 | 391.17 | 4 | 1560.68 | 1561.59 | -0.91 |
| | 521.23 | 3 | 1560.69 | | -0.90 |
| | 781.34 | 2 | 1560.68 | | -0.91 |
| D1-H14 | 425.44 | 4 | 1697.76 | 1698.73 | -0.97 |
| | 566.91 | 3 | 1697.73 | | -1.00 |
| D1-V18 | 542.76 | 4 | 2167.04 | 2167.33 | -0.29 |
| S26-A42 | 799.97 | 2 | 1597.94 | 1598.96 | -1.02 |
| N27-A42 | 756.45 | 2 | 1510.90 | 1511.89 | -0.99 |
| K28-A42 | 699.43 | 2 | 1396.86 | 1397.78 | -0.92 |
| L34-A42 | 429.76 | 2 | 857.52 | 858.11 | -0.59 |
| H14-S26 | 492.92 | 3 | 1475.76 | 1476.65 | -0.89 |
| | 738.88 | 2 | 1475.76 | | -0.89 |
| H14-K28 | 430.48 | 4 | 1717.92 | 1718.93 | -1.01 |
| | 573.63 | 3 | 1717.89 | | -1.04 |
| | 859.95 | 2 | 1717.90 | | -1.03 |
| Q15-K28 | 527.95 | 3 | 1580.85 | 1581.79 | -0.94 |
| | 791.42 | 2 | 1580.84 | | -0.95 |
| L17-K28 | 663.34 | 2 | 1324.68 | 1325.48 | -0.80 |
| Q15-S26 | 670.35 | 2 | 1338.70 | 1339.51 | -0.81 |
| F20-G33 | 689.35 | 2 | 1376.70 | 1377.52 | -0.82 |
| L17-G25 | 497.75 | 2 | 993.50 | 996.13 | -2.63 |
| A30-M35ox | 317.70 | 2 | 633.40 | 632.82 | 0.58 |
| Q15-F20 | 391.23 | 2 | 780.46 | 780.97 | -0.51 |
| H14-F20 | 459.76 | 2 | 917.52 | 918.11 | -0.59 |
| F20-M35 | 811.42 | 2 | 1620.84 | 1621.87 | -1.03 |
| K16-K28 | 364.45 | 4 | 1453.80 | 1453.66 | 0.14 |
| | 485.60 | 3 | 1453.80 | | 0.14 |

[1]Observed Mass – Theoretical Mass

**Table S2.** Secondary fragments resulting from IDE-dependent degradation of Aβ42 (25 μM in 10 mM phosphate buffer, pH 7.4) for 6 hours at 4 °C and substrate-to-enzyme molar ratio of 100:1.

| Fragments | Observed m/z | Charge | Observed Mass | Theoretical Mass | δ (Da)[1] |
|---|---|---|---|---|---|
| D1-H13 | 391.17 | 4 | 1560.68 | 1561.59 | -0.91 |
| | 521.23 | 3 | 1560.69 | | -0.90 |
| | 781.34 | 2 | 1560.68 | | -0.91 |
| D1-H14 | 425.44 | 4 | 1697.76 | 1698.73 | -0.97 |
| | 566.91 | 3 | 1697.73 | | -1.00 |
| D1-V18 | 542.76 | 4 | 2167.04 | 2167.33 | -0.29 |
| S26-A42 | 799.97 | 2 | 1597.94 | 1598.96 | -1.02 |
| N27-A42 | 756.45 | 2 | 1510.90 | 1511.89 | -0.99 |
| K28-A42 | 699.43 | 2 | 1396.86 | 1397.78 | -0.92 |
| L34-A42 | 429.76 | 2 | 857.52 | 858.11 | -0.59 |
| H14-S26 | 492.92 | 3 | 1475.76 | 1476.65 | -0.89 |
| | 738.88 | 2 | 1475.76 | | -0.89 |
| H14-K28 | 430.48 | 4 | 1717.92 | 1718.93 | -1.01 |
| | 573.64 | 3 | 1717.92 | | -1.01 |
| | 859.95 | 2 | 1717.90 | | -1.03 |
| Q15-K28 | 527.95 | 3 | 1580.85 | 1581.79 | -0.94 |
| | 791.42 | 2 | 1580.84 | | -0.95 |
| H14-F20 | 459.76 | 2 | 917.52 | 918.11 | -0.59 |
| L17-K28 | 663.34 | 2 | 1324.68 | 1325.48 | -0.80 |
| Q15-S26 | 670.35 | 2 | 1338.70 | 1339.51 | -0.81 |
| F20-G33 | 689.85 | 2 | 1377.70 | 1377.52 | 0.18 |
| A30-M35ox | 317.70 | 2 | 633.40 | 632.82 | 0.58 |
| Q15-F20 | 391.23 | 2 | 780.46 | 780.97 | -0.51 |
| F19-K28 | 557.26 | 2 | 1112.52 | 1113.19 | -0.67 |
| K16-K28 | 364.45 | 4 | 1453.80 | 1453.66 | 0.14 |
| | 485.60 | 3 | 1453.80 | | 0.14 |
| D7-F19 | 520.26 | 3 | 1557.78 | 1558.71 | -0.93 |
| Y10-F20 | 482.92 | 3 | 1445.76 | 1446.67 | -0.91 |
| F20-M35 | 811.42 | 2 | 1620.84 | 1621.87 | -1.03 |
| A21-G33 | 614.82 | 2 | 1229.64 | 1230.34 | -0.70 |

[1]Observed Mass – Theoretical Mass

**Table S3.** Secondary fragments resulting from IDE-dependent degradation of Aβ42 (25 μM in 10 mM phosphate buffer with 40 μM resveratrol, pH 7.4) for 2 hours at 4 °C and substrate-to-enzyme molar ratio of 100:1.

| Fragments | Observed m/z | Charge | Observed Mass | Theoretical Mass | δ (Da)[1] |
|---|---|---|---|---|---|
| D1-H13 | 391.17 | 4 | 1560.68 | 1561.59 | -0.91 |
| | 521.23 | 3 | 1560.69 | | -0.90 |
| | 781.34 | 2 | 1560.68 | | -0.91 |
| D1-H14 | 425.44 | 4 | 1697.76 | 1698.73 | -0.97 |
| | 566.91 | 3 | 1697.73 | | -1.00 |
| D1-V18 | 542.76 | 4 | 2167.04 | 2167.33 | -0.29 |
| S26-A42 | 799.97 | 2 | 1597.94 | 1598.96 | -1.02 |
| N27-A42 | 756.45 | 2 | 1510.90 | 1511.89 | -0.99 |
| K28-A42 | 699.43 | 2 | 1396.86 | 1397.78 | -0.92 |
| L34-A42 | 429.76 | 2 | 857.52 | 858.11 | -0.59 |
| L34-A42ox | 437.76 | 2 | 873.52 | 874.51 | -0.99 |
| D23-A42 | 623.31 | 3 | 1866.93 | 1870.24 | -3.31 |
| H13-S26 | 405.19 | 4 | 1616.76 | 1613.79 | 2.97 |
| | 539.91 | 3 | 1616.73 | | 2.94 |
| H14-S26 | 492.92 | 3 | 1475.76 | 1476.65 | -0.89 |
| | 738.88 | 2 | 1475.76 | | -0.89 |
| H14-K28 | 430.48 | 4 | 1717.92 | 1718.93 | -1.01 |
| | 573.63 | 3 | 1717.89 | | -1.04 |
| | 859.95 | 2 | 1717.90 | | -1.03 |
| H14-N27 | 398.18 | 4 | 1588.72 | 1590.76 | -2.04 |
| | 530.57 | 3 | 1588.71 | | -2.05 |
| | 795.35 | 2 | 1588.70 | | -2.06 |
| Q15-K28 | 527.95 | 3 | 1580.85 | 1581.79 | -0.94 |
| | 791.42 | 2 | 1580.84 | | -0.95 |
| L17-K28 | 663.34 | 2 | 1324.68 | 1325.48 | -0.80 |
| Q15-S26 | 670.35 | 2 | 1338.70 | 1339.51 | -0.81 |
| F20-G33 | 689.85 | 2 | 1377.70 | 1377.52 | 0.18 |
| F20-V36 | 432.45 | 4 | 1725.80 | 1722.02 | 3.78 |
| | 576.26 | 3 | 1725.78 | | 3.76 |
| L17-G25 | 497.75 | 2 | 993.50 | 996.13 | -2.63 |
| A30-M35ox | 317.70 | 2 | 633.40 | 632.82 | 0.58 |
| Q15-F20 | 391.23 | 2 | 780.46 | 780.97 | -0.51 |
| A2-F19 | 549.77 | 4 | 2195.08 | 2199.41 | -4.33 |
| S26-G38 | 608.31 | 2 | 1214.62 | 1216.46 | -1.84 |
| K16-K28 | 485.26 | 3 | 1452.78 | 1453.66 | -0.88 |
| H14-F20 | 459.76 | 2 | 917.52 | 918.11 | -0.59 |
| F20-G37 | 889.46 | 2 | 1776.92 | 1778.05 | -1.13 |
| F20-M35 | 811.42 | 2 | 1620.84 | 1621.87 | -1.03 |
| Q15-N27 | 727.37 | 2 | 1452.74 | 1453.61 | -0.87 |
| I32-G38ox | 331.72 | 2 | 661.44 | 661.81 | -0.37 |
| R5-L17 | 537.29 | 3 | 1608.87 | 1606.75 | 2.12 |
| F20-L34 | 745.43 | 2 | 1488.86 | 1490.78 | -1.92 |
| F19-V39ox | 700.39 | 3 | 2098.17 | 2098.44 | -0.27 |
| | 1050.08 | 2 | 2098.16 | | -0.28 |

[1]Observed Mass – Theoretical Mass

**Table S4.** Secondary fragments resulting from IDE-dependent degradation of Aβ42 (25 μM in 10 mM phosphate buffer with 40 μM resveratrol, pH 7.4) for 6 hours at 4 °C and substrate-to-enzyme molar ratio of 100:1.

| Fragments | Observed m/z | Charge | Observed Mass | Theoretical Mass | δ (Da)[1] |
|---|---|---|---|---|---|
| D1-H13 | 391.17 | 4 | 1560.68 | 1561.59 | -0.91 |
| | 521.23 | 3 | 1560.69 | | -0.90 |
| | 781.34 | 2 | 1560.68 | | -0.91 |
| D1-H14 | 425.44 | 4 | 1697.76 | 1698.73 | -0.97 |
| | 566.91 | 3 | 1697.73 | | -1.00 |
| D1-V18 | 542.76 | 4 | 2167.04 | 2167.33 | -0.29 |
| S26-A42 | 799.97 | 2 | 1597.94 | 1598.96 | -1.02 |
| N27-A42 | 756.45 | 2 | 1510.90 | 1511.89 | -0.99 |
| L34-A42 | 429.76 | 2 | 857.52 | 858.11 | -0.59 |
| L34-A42ox | 437.76 | 2 | 873.52 | 874.51 | -0.99 |
| K28-A42 | 699.43 | 2 | 1396.86 | 1397.78 | -0.92 |
| H14-S26 | 492.92 | 3 | 1475.76 | 1476.65 | -0.89 |
| | 738.88 | 2 | 1475.76 | | -0.89 |
| H14-K28 | 430.48 | 4 | 1717.92 | 1718.93 | -1.01 |
| | 573.63 | 3 | 1717.89 | | -1.04 |
| | 859.95 | 2 | 1717.90 | | -1.03 |
| H14-N27 | 398.18 | 4 | 1588.72 | 1590.76 | -2.04 |
| | 530.57 | 3 | 1588.71 | | -2.05 |
| | 795.35 | 2 | 1588.70 | | -2.06 |
| Q15-K28 | 527.95 | 3 | 1580.85 | 1581.79 | -0.94 |
| | 791.42 | 2 | 1580.84 | | -0.95 |
| H13-S26 | 405.19 | 4 | 1616.76 | 1613.79 | -2.97 |
| | 539.91 | 3 | 1616.73 | | -2.94 |
| H14-F20 | 459.76 | 2 | 917.52 | 918.11 | -0.59 |
| L17-K28 | 663.34 | 2 | 1324.68 | 1325.48 | -0.80 |
| Q15-S26 | 670.35 | 2 | 1338.70 | 1339.51 | -0.81 |
| F20-G33 | 689.85 | 2 | 1377.70 | 1377.52 | 0.18 |
| F20-V36 | 346.16 | 5 | 1725.80 | 1722.02 | 3.78 |
| | 432.45 | 4 | 1725.80 | | 3.78 |
| | 576.26 | 3 | 1725.78 | | 3.76 |
| L17-G25 | 497.75 | 2 | 993.50 | 996.13 | -2.63 |
| A21-G33 | 615.82 | 2 | 1229.64 | 1230.34 | -0.70 |
| A30-M35ox | 317.70 | 2 | 633.40 | 632.82 | 0.58 |
| A21-M35 | 737.88 | 2 | 1473.76 | 1474.69 | -0.93 |
| E22-M35 | 703.37 | 2 | 1404.74 | 1403.61 | 1.13 |
| S26-M35ox | 511.76 | 2 | 1021.52 | 1020.24 | 1.28 |
| F20-L34 | 745.90 | 2 | 1489.80 | 1490.68 | -0.88 |
| Q15-F20 | 391.23 | 2 | 780.46 | 780.97 | -0.51 |
| S26-G38 | 608.31 | 2 | 1214.62 | 1216.46 | -1.84 |
| Y10-F20 | 482.92 | 3 | 1445.76 | 1446.67 | -0.91 |
| K16-K28 | 485.26 | 3 | 1452.78 | 1453.66 | -0.14 |
| F19-K28 | 557.26 | 2 | 1112.52 | 1113.19 | -0.67 |
| F4-L17 | 439.45 | 4 | 1753.80 | 1752.91 | -0.89 |
| R5-L17 | 537.29 | 3 | 1608.87 | 1606.75 | 2.12 |
| I32-G38ox | 331.72 | 2 | 661.44 | 661.81 | -0.37 |
| F19-V39ox | 700.39 | 3 | 2098.17 | 2098.44 | -0.27 |
| | 1050.08 | 2 | 2098.16 | | -0.28 |

[1]Observed Mass – Theoretical Mass