**Supporting Information**

Main Title: Computational investigation on the effect of Oleuropein aglycone on the α-Synuclein aggregation

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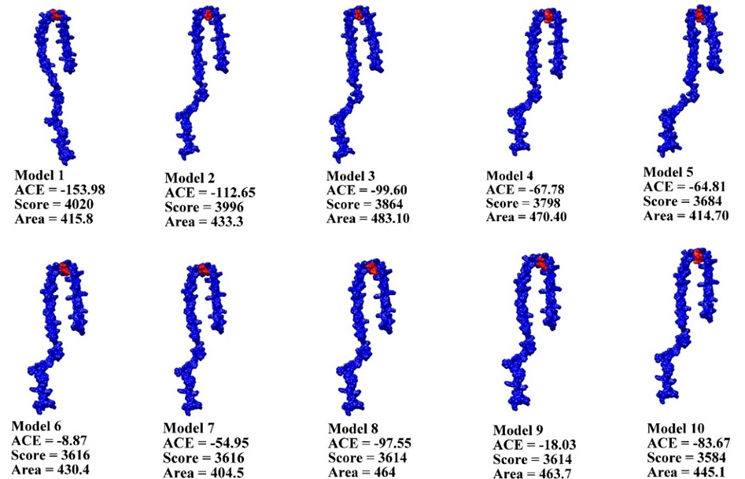
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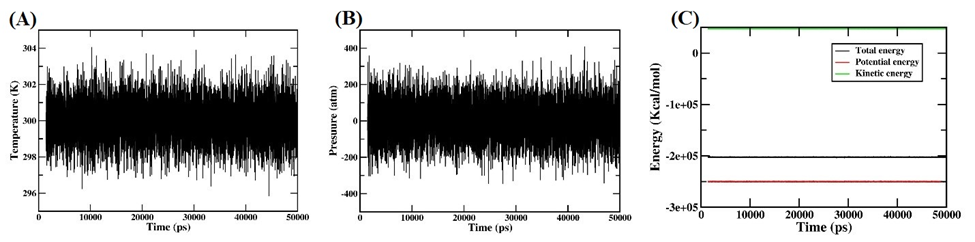
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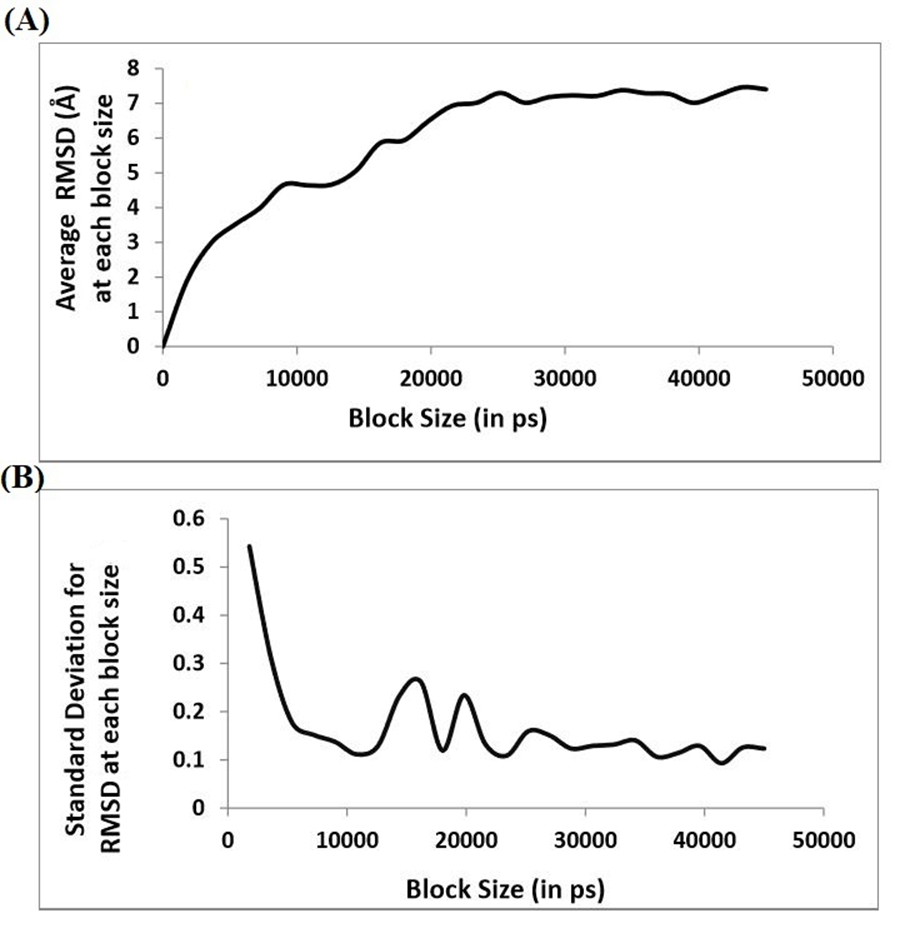
**Supplemtentary figures**

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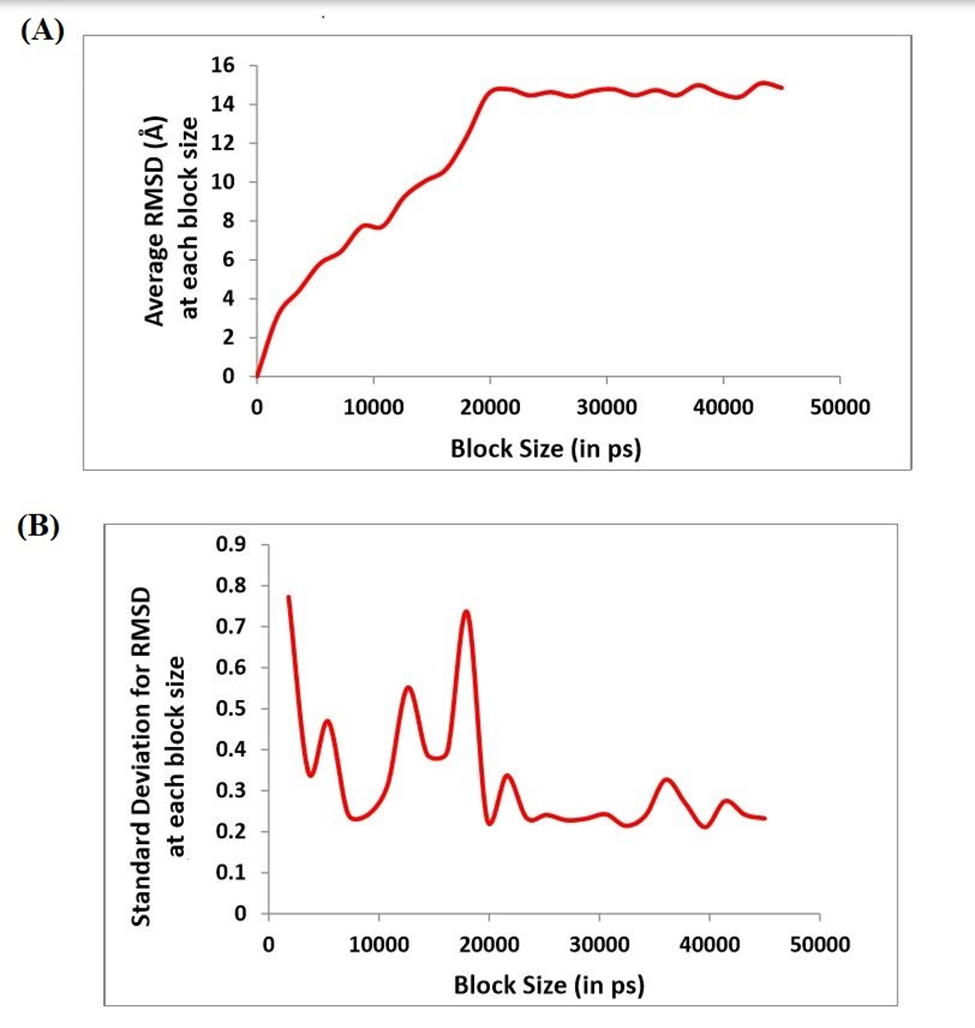
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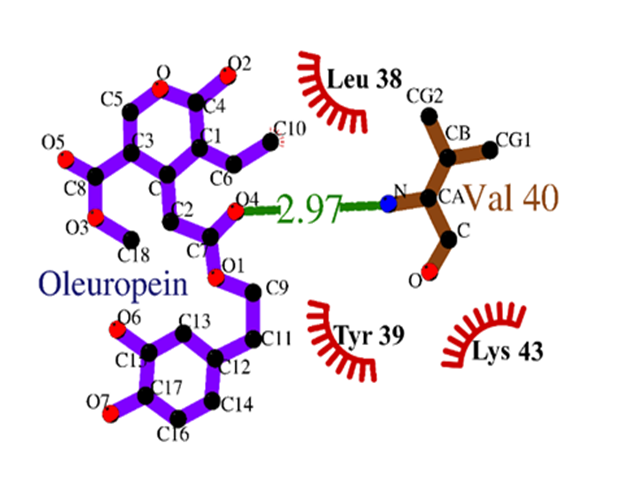
**Figure S2.** (**A)** Temperature, (**B)** Pressure, and (**C)** Energy plots of (α-synuclein + OleA) complex system as a function of simulation time.



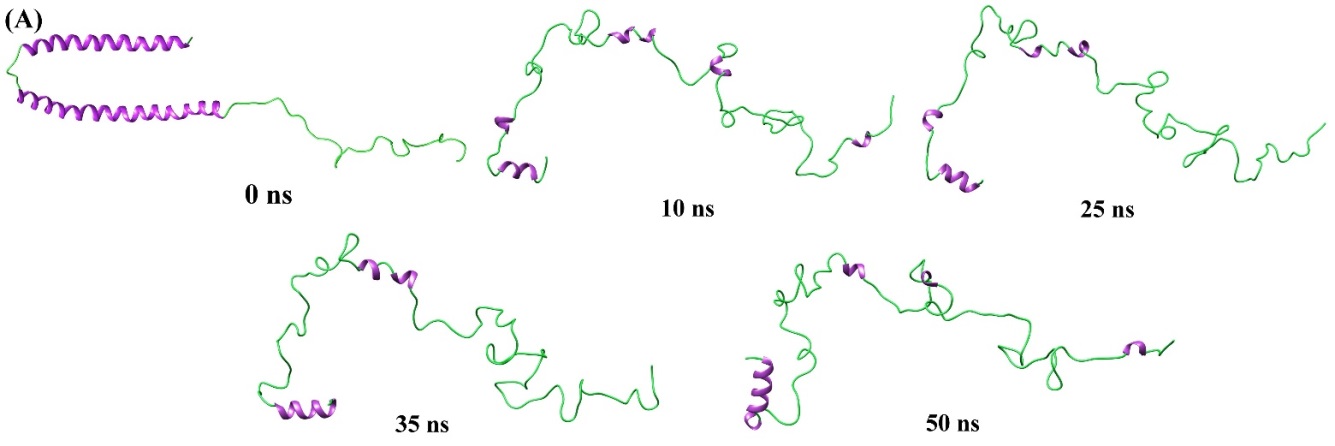
**Figure S3.** A) Average RMSD at each block versus block size in picoseconds B) Standard deviation for the RMSD at each block size versus block size in picoseconds for the α-synuclein (apo) Molecular dynamics trajectory.

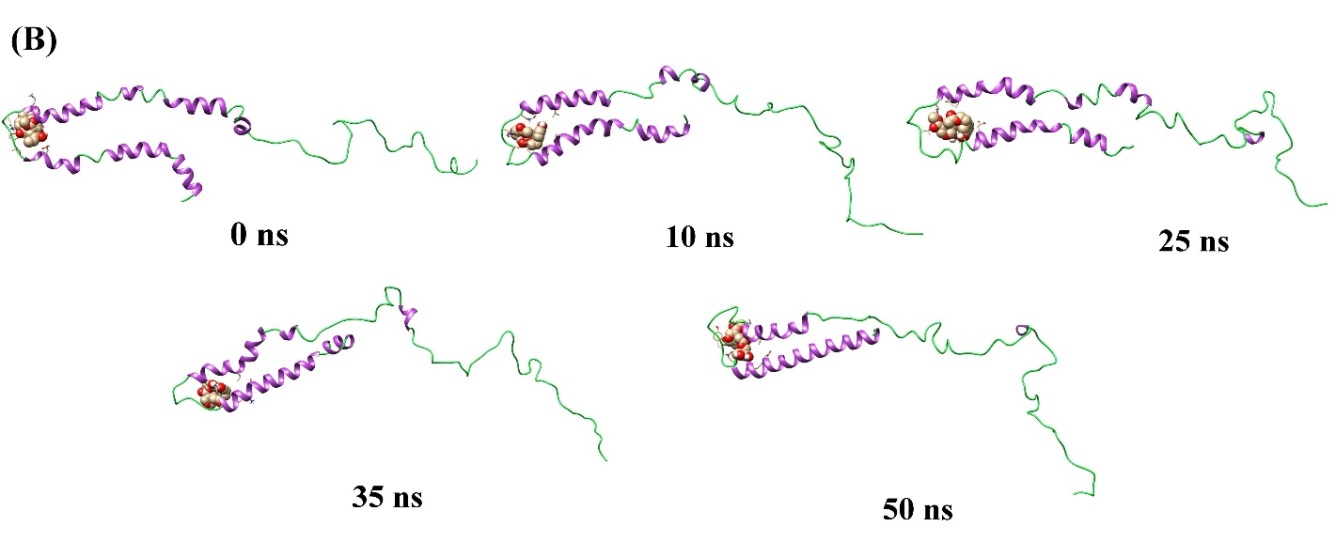


**Figure S4.** A) Average RMSD at each block versus block size in picoseconds B) Standard deviation for the RMSD at each block size versus block size in picoseconds for the (α-synuclein + OleA) complex Molecular dynamics trajectory.

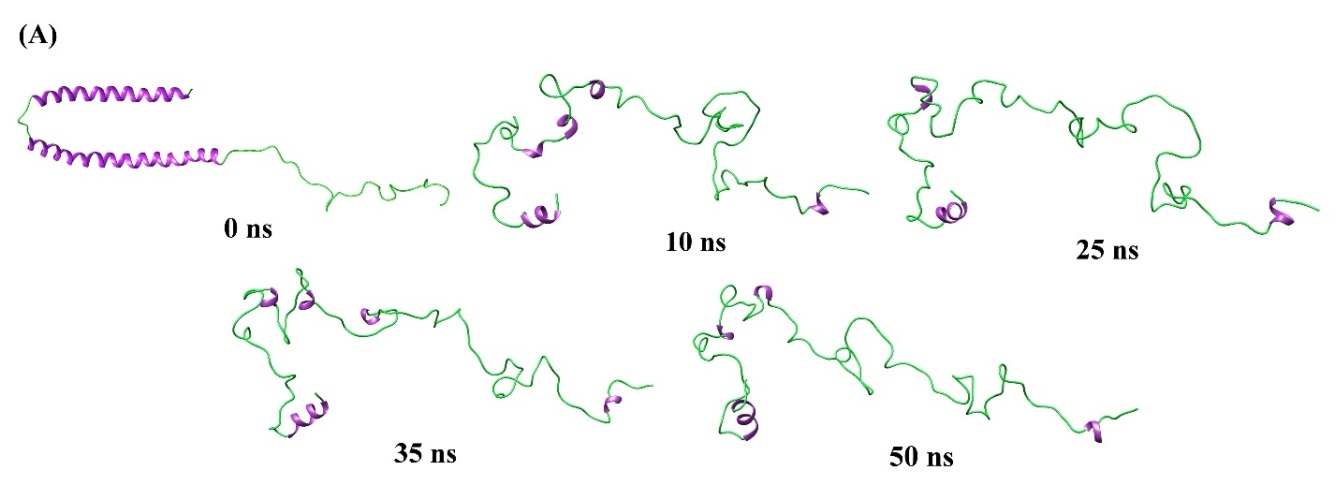


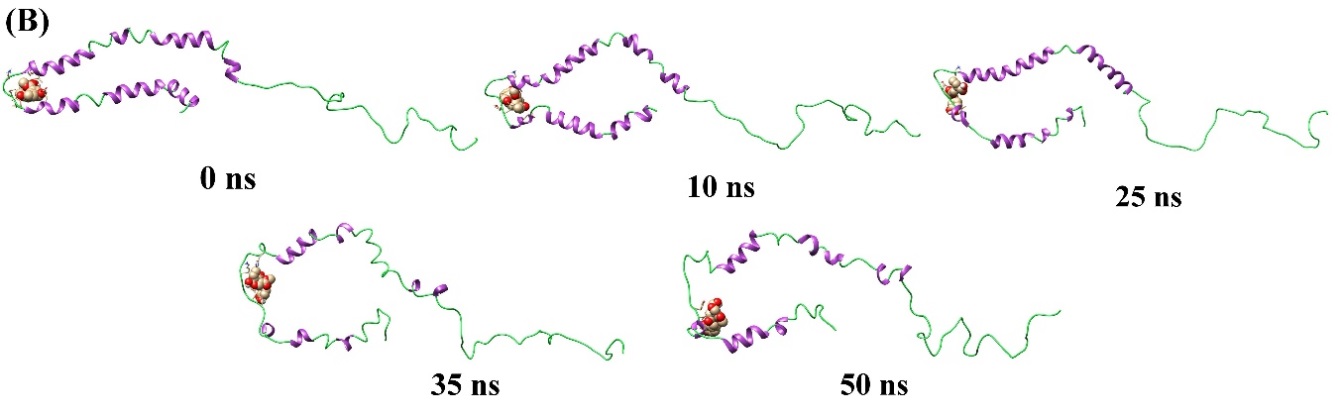
**Figure S5.** Ligplot analysis showing the interaction of hydrophobic residues of α-synuclein with OleA.



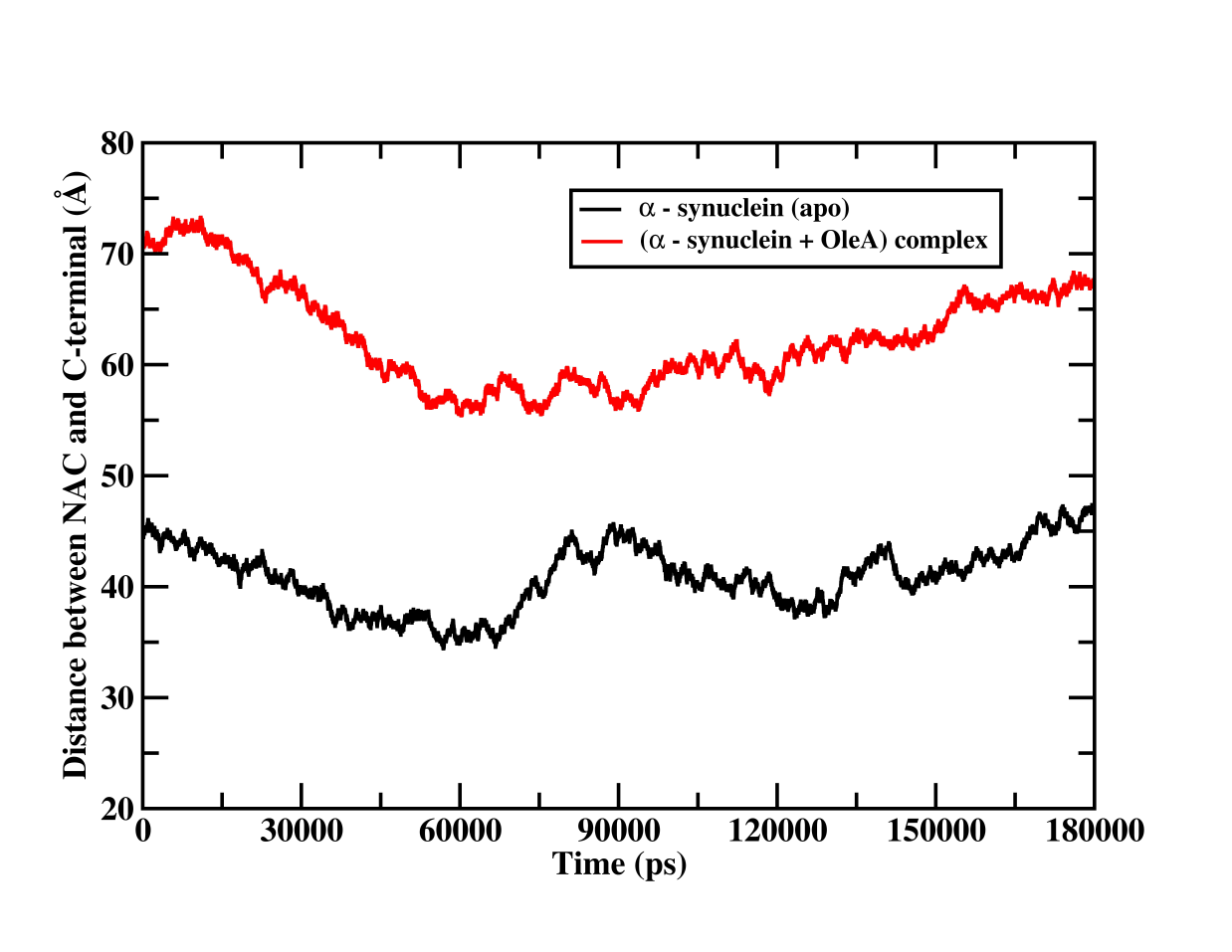


**Figure S6.** Snapshots of the conformers (from simulation-II) of α-synuclein taken at different interval of simulation time (A) α-synuclein (apo), (B) (α-synuclein + OleA) complex.

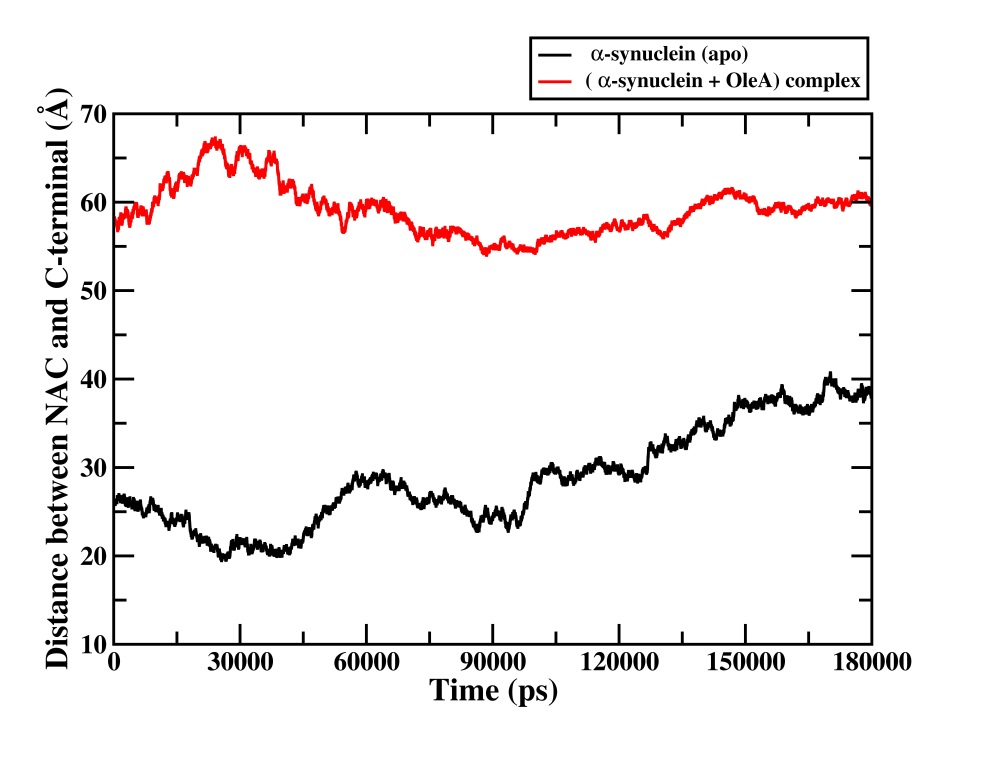




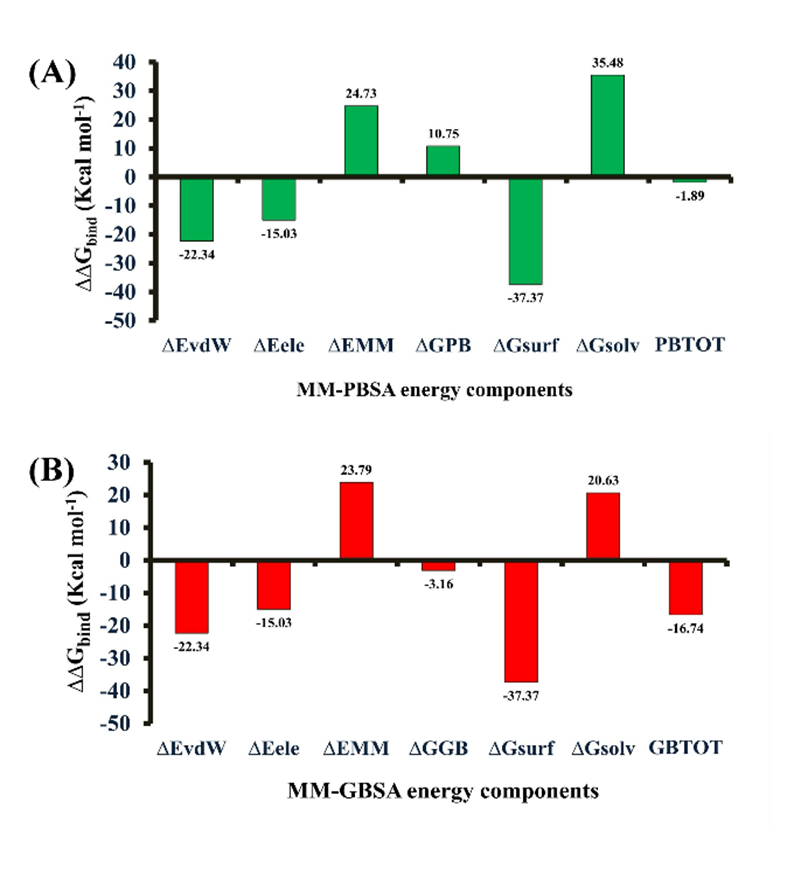
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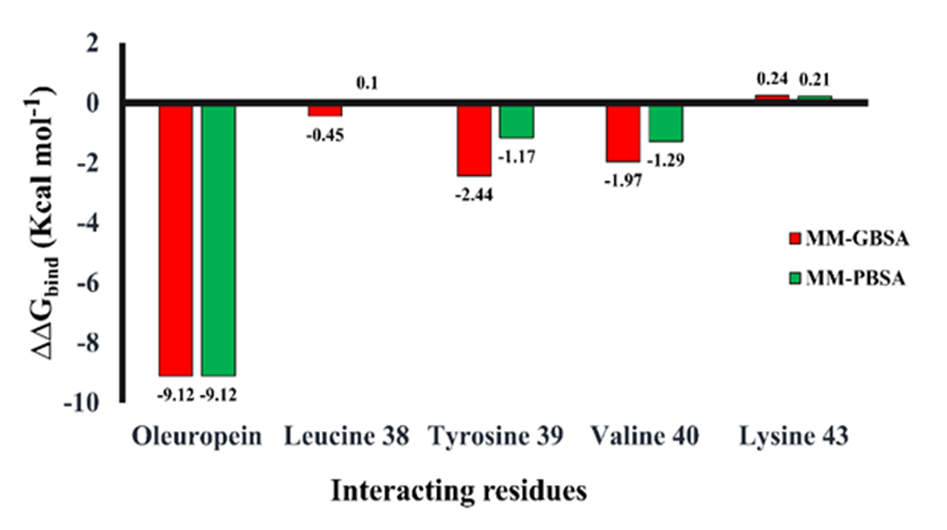
**Figure S8.** Intra-molecular distance analysis (from simulation-II) between NAC and C-terminal domains as a function of simulation time for the α-synuclein (apo) and (α-synuclein + OleA) complex.



**Figure S9.** Intra-molecular distance analysis (from simulation-III) between NAC and C-terminal domains as a function of simulation time for the α-synuclein (apo) and (α-synuclein + OleA) complex.



**Figure S10.** ∆∆Gbind of various energy components in A) MM-PBSA and B) MM-GBSA method of Binding free energy calculation of (α-synuclein + OleA) complex.



**Figure S11.** Per-residue energy decomposition (PRED) plots for the interface residues of ligand (OleA) and receptor α-synuclein calculated by MM-GBSA/PBSA method.

**Supplementary tables**

**Table S1.** Physico-chemical properties of Oleuropein aglycone (OleA)

|  |  |
| --- | --- |
| Chemical structure | C:\Users\user\Desktop\MVS LAB\OLEUROPEIN\imagefly.png |
| Chemical name)  (IUPAC | methyl (2R,3E,4S)-4-{2-[2-(3,4-dihydroxyphenyl)ethoxy]-2-oxoethyl}-3-ethylidene-2-hydroxy-3,4-dihydro-2H-pyran-5-carboxylate |
| SMILES | COC(=O)C1=COC(C(=CC)C1CC(=O)OCCc1ccc(c(c1)O)O)O |
| Molecular formula | C19H22O8 |
| Molecular weight | 378.377 g/mol |
| H-Bond donor | 8 |
| H-Bond acceptor | 3 |
| Log P*c* | 1.34 |
| Rotatable bonds | 8 |
| TPSA (A2) | 122.53 |

TPSA = Topological polar surface area; logP = octanol-water partition coefficients

**Table 2.** Interactions of residues of α-synuclein (Receptor) with OleA(ligand) obtained from Ligplot+ software.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| α-synuclein(Receptor) | | |  | OleA(ligand) | | | |
| Atom name | Residue name | Residue number | < ---> | Atom name | Residue name | Residue number | Bond distance |
| CD2 | TYR | 40 | < ---> | O1 | LIG | 1 | 3.65 |
| CE1 | TYR | 40 | < ---> | O1 | LIG | 1 | 3.80 |
| CE2 | TYR | 40 | < ---> | O1 | LIG | 1 | 3.16 |
| CZ | TYR | 40 | < ---> | O1 | LIG | 1 | 3.32 |
| OH | TYR | 40 | < ---> | O1 | LIG | 1 | 3.76 |
| CA | TYR | 40 | < ---> | O4 | LIG | 1 | 3.37 |
| C | TYR | 40 | < --- > | O4 | LIG | 1 | 3.63 |
| CG | TYR | 40 | < --- > | O4 | LIG | 1 | 3.54 |
| CD2 | TYR | 40 | < --- > | O4 | LIG | 1 | 3.58 |
| N | VAL | 41 | < --- > | O4 | LIG | 1 | 2.97 |
| CA | TYR | 41 | < --- > | O4 | LIG | 1 | 3.83 |
| C | TYR | 40 | < ---> | O1 | LIG | 1 | 3.83 |
| O | TYR | 40 | < ---> | O1 | LIG | 1 | 3.67 |
| CG2 | TYR | 40 | < ---> | O1 | LIG | 1 | 3.79 |
| O | TYR | 40 | < ---> | C2 | LIG | 1 | 3.66 |
| CG | TYR | 40 | < ---> | C2 | LIG | 1 | 3.89 |
| CD1 | TYR | 40 | < ---> | C2 | LIG | 1 | 3.42 |
| CE1 | TYR | 40 | < --- > | C2 | LIG | 1 | 3.39 |
| CZ | TYR | 40 | < --- > | C2 | LIG | 1 | 3.82 |
| CG | TYR | 40 | < --- > | C7 | LIG | 1 | 3.52 |
| CD1 | TYR | 40 | < --- > | C7 | LIG | 1 | 3.59 |
| CE1 | TYR | 40 | < --- > | C7 | LIG | 1 | 3.68 |
| CE2 | TYR | 40 | < --- > | C7 | LIG | 1 | 3.51 |
| CZ | TYR | 40 | < --- > | C7 | LIG | 1 | 3.65 |
| CE2 | TYR | 40 | < --- > | C9 | LIG | 1 | 3.52 |
| O | TYR | 40 | < --- > | C10 | LIG | 1 | 2.96 |
| CE2 | TYR | 40 | < --- > | C11 | LIG | 1 | 3.85 |
| C | LYS | 44 | < --- > | C18 | LIG | 1 | 3.80 |
| O | LYS | 44 | < --- > | C18 | LIG | 1 | 3.09 |

**Table S3.** Intra- molecular Hydrogen bond occupancy between NAC and C-terminal domain of α-synuclein (apo).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Acceptor | Donor | Frac | AvgDist | AvgAng |
|  | LYS\_98@HG2 | VAL\_96@CB | 0.0018 | 2.9256 | 139.8006 |
|  | LYS\_98@H | VAL\_96@CB | 0.0014 | 2.894 | 146.0744 |
|  | LYS\_97@HE3 | PHE\_95@CE2 | 0.0009 | 2.9101 | 146.5537 |
|  | LYS\_98@H | VAL\_96@CG2 | 0.0009 | 2.9193 | 148.7936 |
|  | GLN\_100@HE21 | VAL\_96@CG2 | 0.0005 | 2.8565 | 143.1733 |
|  | LYS\_97@HG3 | PHE\_95@CE2 | 0.0004 | 2.9465 | 142.9428 |
|  | LYS\_98@H | VAL\_96@CG2 | 0.0004 | 2.8978 | 142.1204 |
|  | GLN\_100@HE22 | VAL\_96@CG2 | 0.0004 | 2.8627 | 147.7553 |
|  | LYS\_97@HG3 | PHE\_95@CE1 | 0.0003 | 2.9669 | 140.9906 |
|  | LYS\_98@HE2 | VAL\_96@CG2 | 0.0003 | 2.9483 | 144.263 |
|  | LYS\_98@HE2 | VAL\_96@CG1 | 0.0003 | 2.8777 | 139.3384 |
|  | ASP\_99@HB2 | VAL\_96@CB | 0.0003 | 2.9706 | 140.7942 |
|  | GLN\_100@HG3 | PHE\_95@CE2 | 0.0003 | 2.9164 | 139.2789 |
|  | LYS\_97@HG2 | PHE\_95@CE2 | 0.0002 | 2.9469 | 137.6289 |
|  | LYS\_97@HE2 | PHE\_95@CE1 | 0.0002 | 2.9581 | 150.7708 |
|  | LYS\_98@HE2 | VAL\_96@CG1 | 0.0002 | 2.8796 | 143.8116 |
|  | GLN\_100@HE22 | VAL\_96@CG1 | 0.0002 | 2.9376 | 143.6786 |
|  | LYS\_97@HB2 | PHE\_95@CE1 | 0.0001 | 2.9183 | 141.9421 |
|  | LYS\_97@HB2 | PHE\_95@CE2 | 0.0001 | 2.9904 | 141.6481 |
|  | LYS\_97@HG3 | PHE\_95@CD1 | 0.0001 | 2.9718 | 144.6032 |
|  | LYS\_97@HE2 | PHE\_95@CZ | 0.0001 | 2.9362 | 140.0901 |
|  | LYS\_97@HE3 | PHE\_95@CE1 | 0.0001 | 2.9397 | 135.6953 |

**Table S4.** Intra-molecular Hydrogen bond occupancy between NAC and C-terminal domain of (α-synuclein + OleA) complex.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Acceptor | Donor | Frac | AvgDist | AvgAng |
| GLU\_105@OE2 | SER\_87@OG | 0.179 | 2.6941 | 164.734 |
| GLU\_105@OE1 | SER\_87@N | 0.1048 | 2.8667 | 158.75 |
| GLU\_104@OE2 | SER\_87@OG | 0.0952 | 2.7018 | 164.754 |
| GLU\_104@OE1 | SER\_87@OG | 0.0558 | 2.6918 | 163.688 |
| GLU\_105@OE1 | SER\_87@OG | 0.044 | 2.7219 | 163.493 |
| GLU\_104@OE2 | SER\_87@N | 0.015 | 2.8303 | 152.884 |
| LYS\_96@HE3 | ALA\_89@CB | 0.0092 | 2.9177 | 151.355 |
| LYS\_96@HE3 | ALA\_89@CB | 0.0034 | 2.9099 | 145.029 |
| GLN\_99@HE22 | ALA\_89@CB | 0.0014 | 2.8935 | 142.496 |
| LYS\_96@HE3 | ALA\_89@CB | 0.0012 | 2.8848 | 148.269 |
| GLU\_105@OE2 | SER\_87@N | 0.0012 | 2.9551 | 142.979 |
| LYS\_96@HD3 | ALA\_89@CB | 0.001 | 2.8931 | 139.063 |
| LYS\_96@HD3 | ALA\_89@CA | 0.001 | 2.9396 | 141.174 |
| LYS\_96@HZ3 | THR\_75@CG2 | 0.001 | 2.8856 | 143.181 |
| LYS\_96@HE2 | THR\_92@CG2 | 0.0008 | 2.8692 | 154.939 |
| LYS\_96@HE2 | THR\_92@CG2 | 0.0008 | 2.9365 | 148.028 |
| LYS\_96@HZ3 | THR\_75@CG2 | 0.0006 | 2.924 | 139.655 |
| GLN\_99@HE21 | ALA\_89@CB | 0.0006 | 2.8379 | 138.273 |
| GLN\_99@HE22 | ALA\_90@CA | 0.0006 | 2.9409 | 149.404 |
| LYS\_96@HB2 | ALA\_89@CB | 0.0004 | 2.9503 | 135.449 |
| LYS\_96@HB3 | ALA\_89@CB | 0.0004 | 2.9771 | 141.74 |
| LYS\_96@HD2 | ALA\_89@CB | 0.0004 | 2.9654 | 147.532 |
| LYS\_96@HD2 | ALA\_89@CB | 0.0004 | 2.9523 | 150.409 |
| GLU\_104@HG3 | ALA\_89@CB | 0.0004 | 2.936 | 135.334 |
| GLU\_105@CD | SER\_87@OG | 0.0004 | 2.9799 | 159.428 |

**Table S5:** The various components of the Binding Free Energy (kcal mol-1) calculated by Molecular Mechanics/Generalized Borne Surface Area (MM-GBSA) and Molecular Mechanics/Poisson−Boltzmann Surface Area (MM-PBSA) method between (α-synuclein+OleA) complex (for Simulation II)..

1. **MM-GBSA calculation**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Energy components** | **COMPLEX** | **LIGAND** | **RECEPTOR** | **DELTA** |
| **Energy (kcal mol-1)** | **Energy (kcal mol-1)** | **Energy (kcal mol-1)** | **Energy (kcal mol-1)** |
| **EvdW** | 664.61 | -4.23 | -635.98 | -24.40 |
| **Eele** | -8984.29 | 1.36 | -8950.26 | -35.39 |
| **EGB** | -4160.73 | -34.63 | -4170.14 | 44.04 |
| **ESURF** | 95.96 | 3.85 | 95.95 | -3.83 |
| **Ggas** | -9648.90 | -2.87 | -9586.24 | -59.79 |
| **Gsolv** | -4064.76 | -30.78 | -4074.19 | 40.20 |
| **GBTOTAL** | -13713.67 | -33.65 | -13660.43 | -19.59 |
| **TSTRA** | 16.27 | 16.25 | 13.02 | -12.99 |
| **TSROT** | 17.87 | 17.62 | 10.77 | -10.53 |
| **TSVIB** | 1647.97 | 1593.56 | 31.47 | 22.94 |
| **TSTOT** | 1682.11 | 1627.43 | 55.26 | -0.58 |
| **∆Gbind(kcal mol-1)** | | | | **-19.01** |

Electrostatic energy (**Eele**); van der Waals contribution (**Evdw**); total gas phase energy (**Ggas**); nonpolar contribution to the solvation free energy (**ESURF**); the electrostatic contribution to the solvation free energy (**EGB**); sum of nonpolar and polar contributions to solvation (**Gsolv**); final estimated binding free energy (**GBTOTAL**); translational energy (**TSTRA**); rotational energy (**TSROT**); vibrational energy (**TSVIB**), total entropic contribution (**TSTOT**); binding free energy (**ΔGbind**).

1. **MM-PBSA calculation**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Energy components** | **COMPLEX** | **LIGAND** | | **RECEPTOR** | | **DELTA** | |
| **Energy (kcal mol-1)** | | **Energy (kcal mol-1)** | | **Energy (kcal mol-1)** | | **Energy (kcal mol-1)** |
| **EvdW** | -664.61 | | -4.23 | | -635.98 | | -24.40 |
| **Eele** | -8984.29 | | 1.36 | | -8950.26 | | -35.39 |
| **EPB** | -4213.35 | | -37.70 | | -4220.05 | | 44.39 |
| **ESURF** | 232.96 | | 1.58 | | 219.74 | | 11.91 |
| **Ggas** | -9648.90 | | -2.87 | | -9586.24 | | -59.79 |
| **Gsolv** | -3980.40 | | -36.13 | | -4000.58 | | 56.30 |
| **PBTOTAL** | -13629.31 | | -38.99 | | -13586.82 | | -3.49 |
| **TSTRA** | 16.27 | | 16.25 | | 13.02 | | -12.99 |
| **TSROT** | 17.87 | | 17.62 | | 10.77 | | -10.53 |
| **TSVIB** | 1647.97 | | 1593.56 | | 31.47 | | 22.94 |
| **TSTOT** | 1682.11 | | 1627.43 | | 55.26 | | -0.58 |
| **∆Gbind(kcal mol-1)** | | | | | | | **-2.91** |

Electrostatic energy (**Eele**); van der Waals contribution (**Evdw**); total gas phase energy (**Ggas**); nonpolar contribution to the solvation free energy (**ESURF**); the electrostatic contribution to the solvation free energy (**EPB**); sum of nonpolar and polar contributions to solvation (**Gsolv**); final estimated binding free energy (**PBTOTAL**); translational energy (**TSTRA**); rotational energy (**TSROT**); vibrational energy (**TSVIB**), total entropic contribution (**TSTOT**); binding free energy (**ΔGbind**).

**Table S6:** The various components of the Binding Free Energy (kcal mol-1) calculated by Molecular Mechanics/Generalized Borne Surface Area (MM-GBSA) and Molecular Mechanics/Poisson−Boltzmann Surface Area (MM-PBSA) method between (α-synuclein+OleA) complex (for Simulation III).

1. **MM-GBSA calculation**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Energy components** | **COMPLEX** | **LIGAND** | **RECEPTOR** | **DELTA** |
| **Energy (kcal mol-1)** | **Energy (kcal mol-1)** | **Energy (kcal mol-1) ± SD** | **Energy (kcal mol-1) ± SD** |
| **EvdW** | -675.67 | -4.83 | -643.08 | -27.76 |
| **Eele** | -8887.38 | 1.39 | -8867.49 | -21.29 |
| **EGB** | -4267.36 | -34.38 | -4264.44 | 31.46 |
| **ESURF** | 95.53 | 3.84 | 95.90 | -4.22 |
| **Ggas** | -9563.05 | -3.43 | -9510.57 | -49.05 |
| **Gsolv** | -4171.83 | -30.54 | -4168.54 | 27.25 |
| **GBTOTAL** | -13734.88 | -33.97 | -13679.11 | -21.79 |
| **TSTRA** | 16.27 | 13.02 | 16.25 | -12.99 |
| **TSROT** | 17.88 | 10.77 | 17.67 | -10.56 |
| **TSVIB** | 1668.37 | 31.43 | 1603.22 | 33.72 |
| **TSTOT** | 1702.53 | 55.22 | 1637.14 | 10.17 |
| **∆Gbind(kcal mol-1)** | | | | **-31.96** |

Electrostatic energy (**Eele**); van der Waals contribution (**Evdw**); total gas phase energy (**Ggas**); nonpolar contribution to the solvation free energy (**ESURF**); the electrostatic contribution to the solvation free energy (**EGB**); sum of nonpolar and polar contributions to solvation (**Gsolv**); final estimated binding free energy (**GBTOTAL**); translational energy (**TSTRA**); rotational energy (**TSROT**); vibrational energy (**TSVIB**), total entropic contribution (**TSTOT**); binding free energy (**ΔGbind**).

1. **MM-PBSA calculation**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Energy components** | **COMPLEX** | **LIGAND** | | **RECEPTOR** | | **DELTA** | |
| **Energy (kcal mol-1)** | | **Energy (kcal mol-1)** | | **Energy (kcal mol-1)** | | **Energy (kcal mol-1)** |
| **EvdW** | -675.67 | | -4.83 | | -643.08 | | -27.76 |
| **Eele** | -8887.38 | | 1.39 | | -8867.49 | | -21.29 |
| **EPB** | -4328.55 | | -36.73 | | -4326.53 | | 34.71 |
| **ESURF** | 237.88 | | 1.51 | | 222.76 | | 13.46 |
| **Ggas** | -9563.05 | | -3.43 | | -9510.57 | | -49.05 |
| **Gsolv** | -4090.67 | | -35.23 | | -4103.77 | | 48.32 |
| **PBTOTAL** | 13653.73 | | -38.66 | | -13614.34 | | -0.73 |
| **TSTRA** | 16.27 | | 13.02 | | 16.25 | | -12.99 |
| **TSROT** | 17.88 | | 10.77 | | 17.67 | | -10.56 |
| **TSVIB** | 1668.37 | | 31.43 | | 1603.22 | | 33.72 |
| **TSTOT** | 1702.53 | | 55.22 | | 1637.14 | | 10.17 |
| **∆Gbind(kcal mol-1)** | | | | | | | **-10.90** |

Electrostatic energy (**Eele**); van der Waals contribution (**Evdw**); total gas phase energy (**Ggas**); nonpolar contribution to the solvation free energy (**ESURF**); the electrostatic contribution to the solvation free energy (**EPB**); sum of nonpolar and polar contributions to solvation (**Gsolv**); final estimated binding free energy (**PBTOTAL**); translational energy (**TSTRA**); rotational energy (**TSROT**); vibrational energy (**TSVIB**), total entropic contribution (**TSTOT**); binding free energy (**ΔGbind**).