In Silico Investigation of Phytoconstituents from Indian Medicinal Herb '*Tinospora cordifolia* (Giloy)' against SARS-CoV-2 (COVID-19) by Molecular Dynamics Approach

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Keywords: COVID-19, SARS-CoV-2, *Tinospora cordifolia*, berberine, $3CL^{pro}$, β-sitosterol

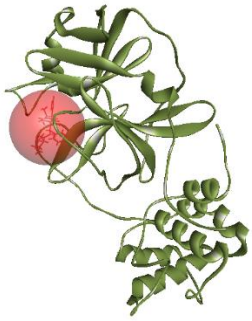
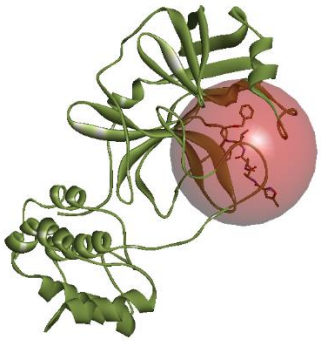
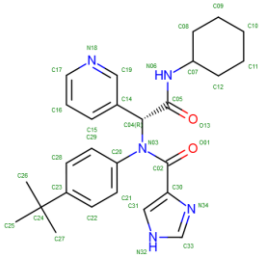
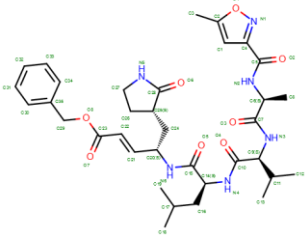
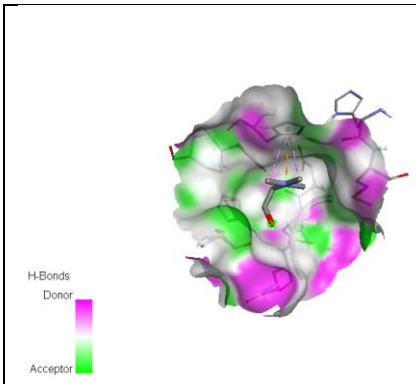
Protein: 3CL^{pro} (PDBID: 6W63)	**Protein: 3CL^{pro} (PDBID: 6LU7)**
Classification: VIRAL PROTEIN/INHIBITOR, main protease bound to potent broad-spectrum non-covalent inhibitor X77	Classification: VIRAL PROTEIN, main protease in complex with an inhibitor N3
Organism(s): Severe acute respiratory syndrome coronavirus 2	**Organism(s):** Severe acute respiratory syndrome coronavirus 2, synthetic construct
Molecule: 3C-like proteinase, **Mutation(s): 0**	Molecule: main protease **Mutation(s):** 0
Chains:A SequenceLength: 306 **Gene Names:** rep, 1a-1b	**Chains:** A **SequenceLength:** 306 **GeneNames:** rep, 1a-1b
X-RAY DIFFRACTION DATA **Resolution:** 2.10 Å **R-Value Free:** 0.221 **R-Value Work:** 0.150 **R-Value Observed:** 0.157 **Space Group: P 2_1 2_1 2**	X-RAY DIFFRACTION DATA **Resolution:** 2.16 Å **R-Value Free:** 0.235 **R-Value Work:** 0.202 **R-Value Observed:** 0.204 **Space Group: C 1 2 1**
Length (Å) Angle (°) **a = 45.05 α = 90** **b = 63.84 β = 90** **c = 106.588 γ = 90**	**Length (Å) Angle (°)** a = 97.931 α = 90 b = 79.477 β = 114.55 c = 51.803 γ = 90
Macromolecule Content Total Structure Weight: 34.29 kDa Atom Count: 4995 Residue Count: 305 Unique protein chains: 1	**Macromolecule Content** Total Structure Weight: 34.51 kDa Atom Count: 2500 Residue Count: 312 Unique protein chains: 2
	
 Native ligand	 Native ligand
C_{27} H_{33} N_5 O_2	X77

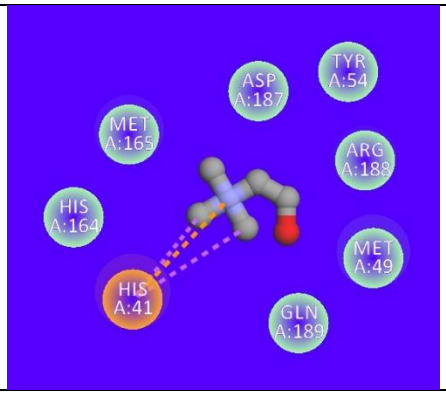
Table SD1: Configuration required of target proteins for simulation.

A

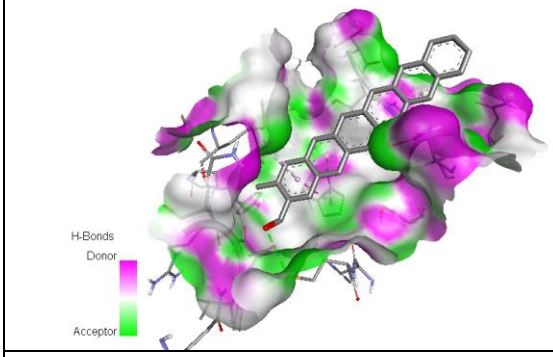
B



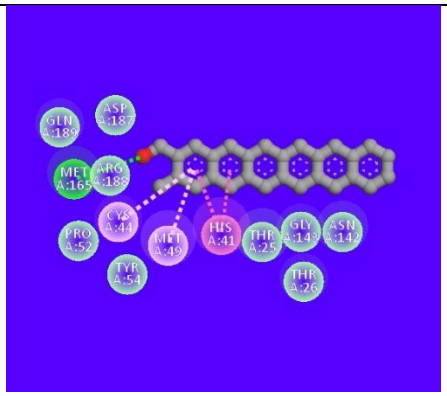
3D: Choline:6W63



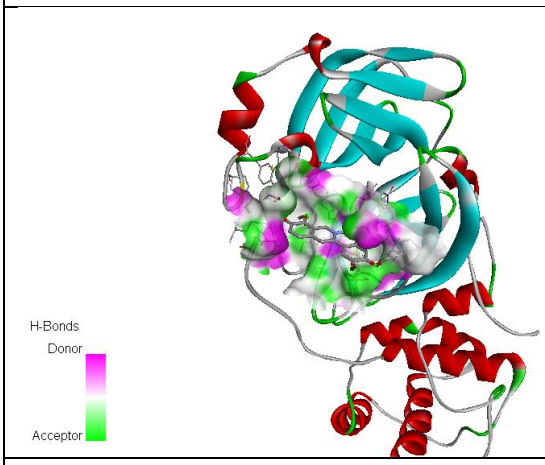
2D: Choline: 6W63



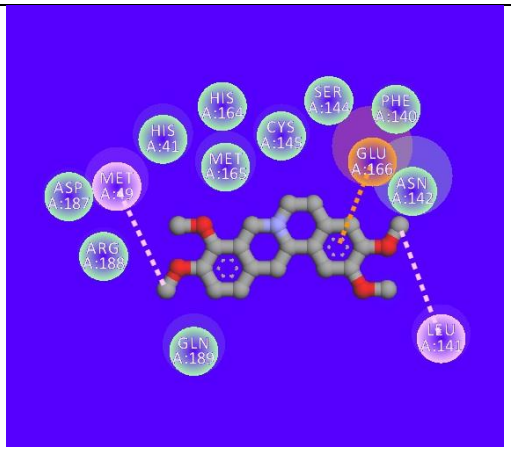
3D: octacosanol:6W63



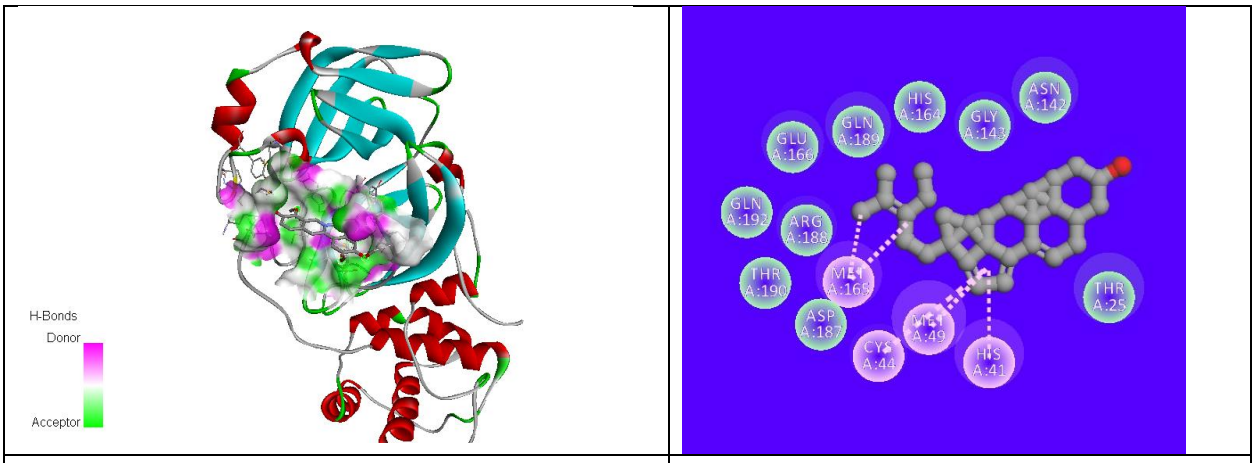
2D: octacosanol: 6W63



3D: tetrahydropalmatine:6W63



2D: tetrahydropalmatine: 6W63



3D: β-sitosterol:6W63	2D: β-sitosterol: 6W63

Figure SD2. Donor: acceptor surface and possible types of interactions in best pose structures obtained from molecular docking for different ligands with COVID-19 protease enzyme $3CL^{pro}$ (6W63).

Ligand	Best Binding affinity (kcal/mole)	Hydrogen bonded interaction (protein donor: ligand acceptor, distance in Å)	Hydrophobic interaction (protein donor: ligand acceptor, distance in Å)	Dipole moment (debye)	Drieding energy between protein and ligand	Inhibition constant (M)
Berberine	-7.7	(A:THR24:HG1 - :UNK0:O, 2.9335)	A:HIS41 - :UNK0, 3.86746 A:HIS41 - :UNK0, 3.85981 :UNK0 - A:CYS145, 5.40468	1.677	426.855	2.23×10^{-6}
β-sitosterol	-8.0		A:CYS44 - :UNK0, 5.02829 A:MET49 - :UNK0, 4.7919 A:MET165 - :UNK0, 4.24509 :UNK0:C - A:MET165, 4.39444 A:HIS41 - :UNK0, 4.30937	1.473	1,284.01	1.34×10^{-6}
Choline	-3.3		:UNK0:C - A:HIS41, 3.6805 :UNK0:C - A:HIS41, 3.91798	4.177	103.961	3.79×10^{-3}
Tetrahydropalmatine	-6.4	:UNK0:C - A:MET49:O, 3.53709	A:HIS41 - :UNK0, 3.70768 A:THR24:C,O;THR25:N - :UNK0, 5.01159	2.669	373.597	2.01×10^{-5}
octacosanol	-7.1	A:ASN119:HD21 - :UNK0:O, 2.1903	A:THR25:CG2 - :UNK0, 3.80725 A:HIS41 - :UNK0, 4.09107 A:HIS41 - :UNK0, 4.46232 A:HIS41 - :UNK0, 5.27182 :UNK0 - A:CYS44, 5.37368 :UNK0 - A:MET49, 5.27559 :UNK0 - A:MET49, 5.22475	1.253	414.219	6.16×10^{-6}

Table SD3: Interaction detail for different ligands: berberine, β-sitosterol, choline, tetrahydropalmatine and octacosanol with receptor protein II (6W63)

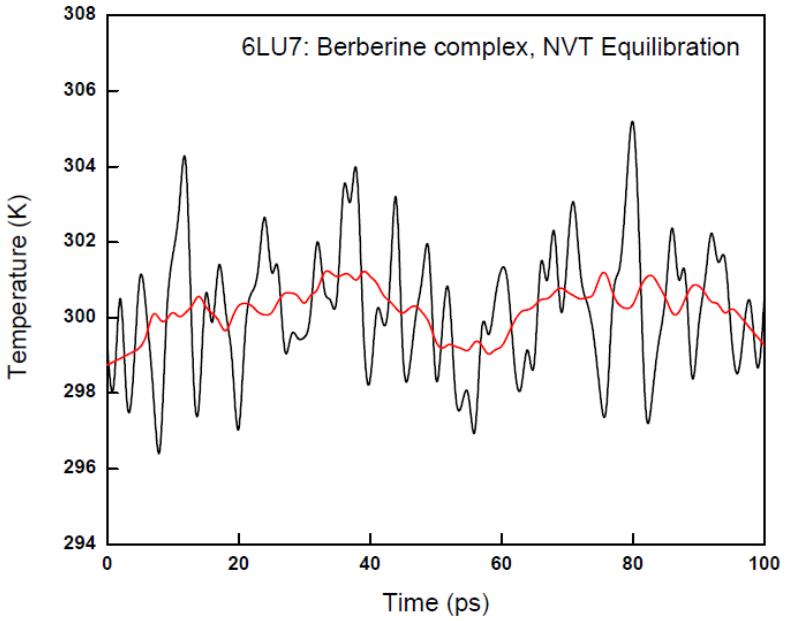


Figure SD4: Temperature progression data by MD simulation for 6LU7: berberine complex in water environment.

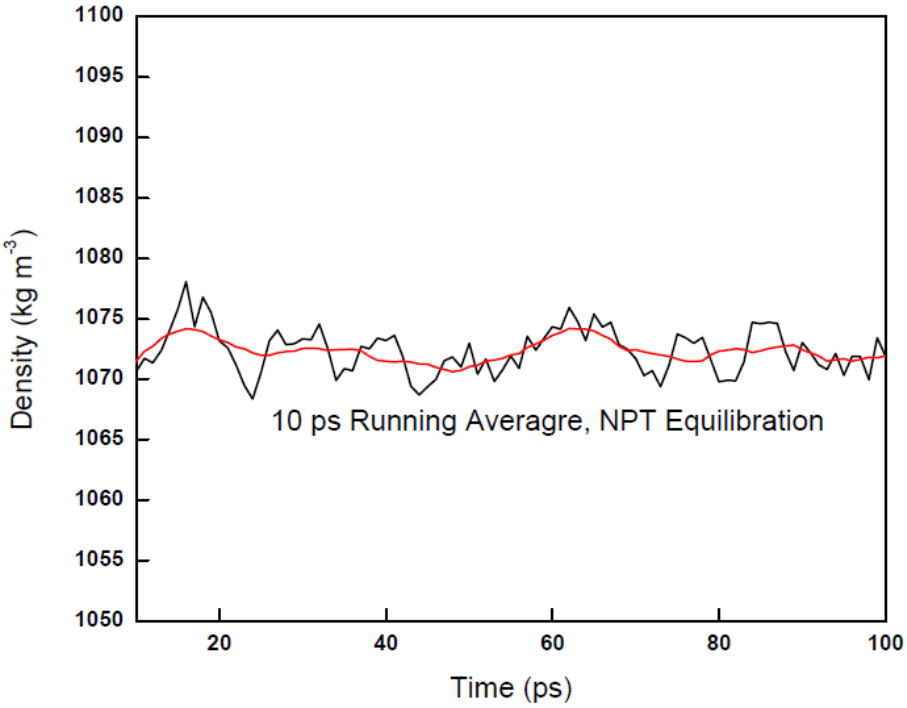


Figure SD5: Density progression data by MD simulation for 6LU7: berberine complex in water environment.

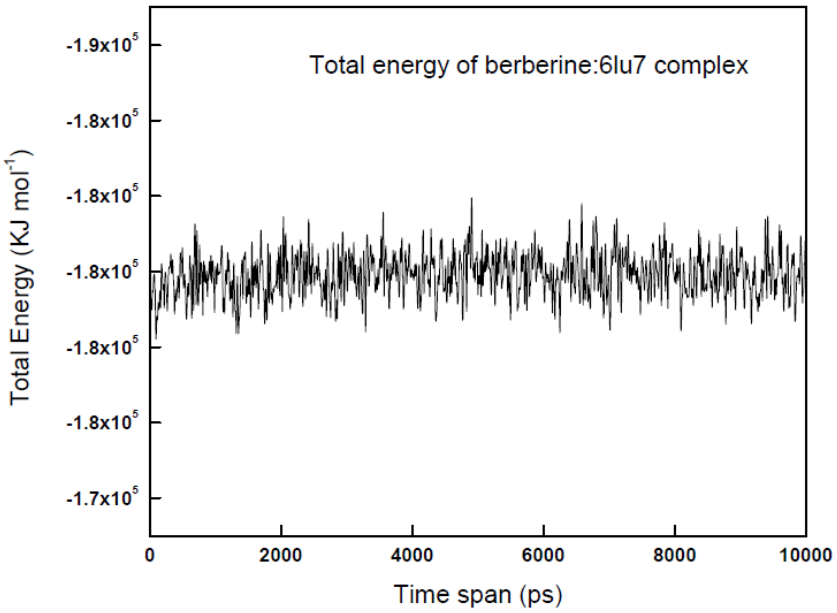


Figure SD6: Total energy by MD simulation for 6LU7: berberine complex in water environment.

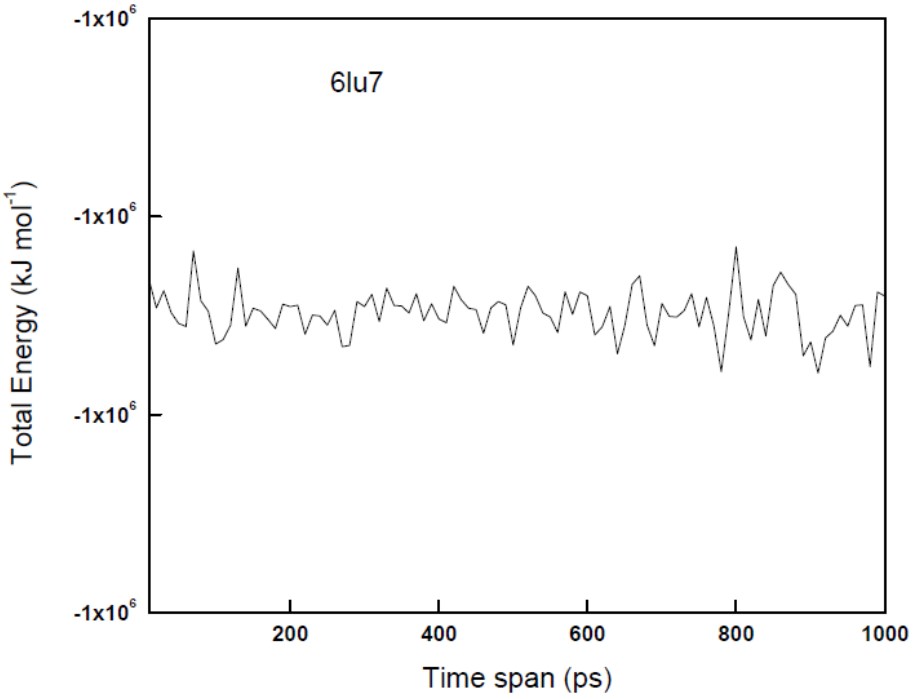


Figure SD7: Total energy by MD simulation for 6LU7 in water environment.

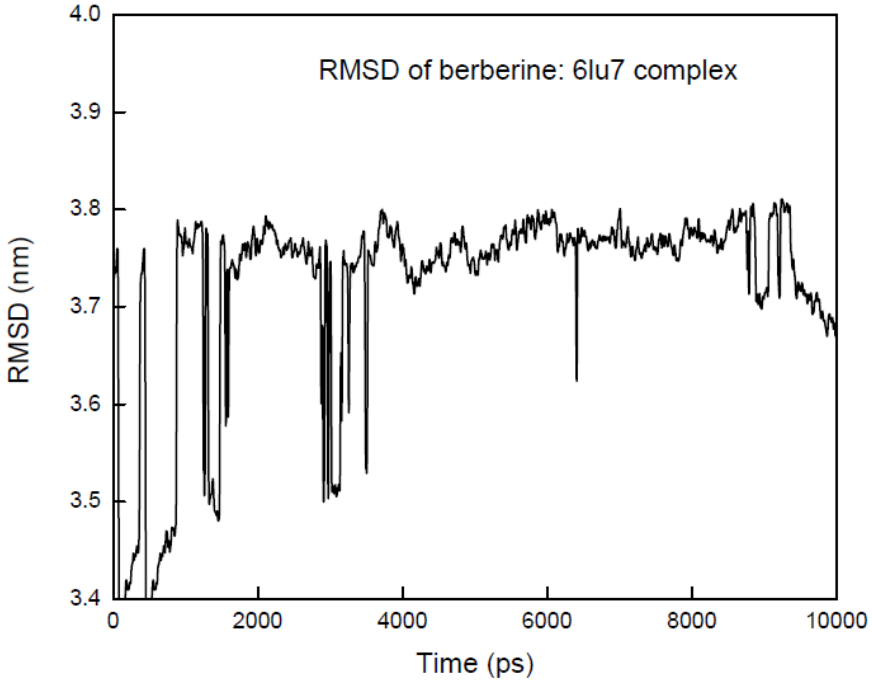


Figure SD8: RMSD of berberine: 6LU7 complex.