Electronic Supplementary Information

Antiviral Activities of Natural Compounds and Ionic Liquids to Inhibit the Mpro of SARS-CoV-2: A Computational Approach

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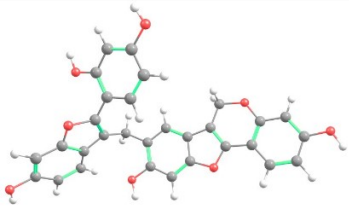
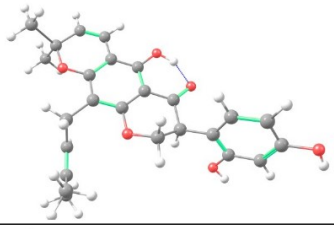
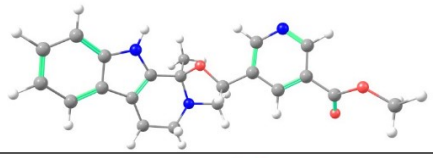
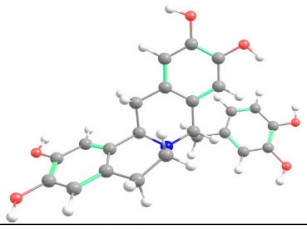
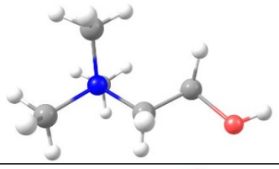
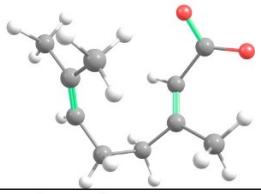
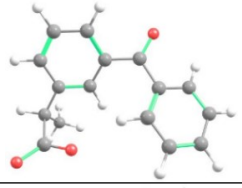
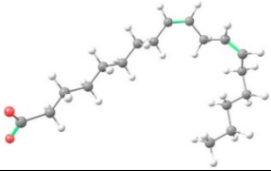
Electronic Supplementary Information (ESI): Docking energies of ILs with Mpro, the average values of RMSD, RMSF, Rg and Hydrogen bonding interactions, RMSF plots and binding free energies of Mpro with cholinium-based ILs and natural compounds are shown.

Mpro-Lopinavir complex:

The optimized lopinavir structure was docked with Mpro. The docking score is -7.7 kcal/mol and the binding sites were shown in **Fig. S1.** The Mpro residues of His-163, His-164 and Gln-189 form non-conventional H-bonding interactions with lopinavir at the distance of 2.6, 2.6 and 2.1 Å. The π-π interactions arise between lopinavir and His-41 of Mpro. The ADMET properties of lopinavir were displayed in **Table S2.**

We performed MD simulation for the Mpro-lopinavir complex for 100 ns. The same MD protocol which is mentioned in the manuscript, used for MD simulations. The RMSD, RMSF plots show the deviations and fluctuations of each residue which is shown in **Fig. S2.** It revealed that the lopinavir strongly enhances the stability of Mpro. The average H-bonding interactions of the Mpro-lopinavir complex is 1, and lopinavir forms van der Waals interactions with the Mpro. We conclude that our selected natural products and cholinium-based ILs improve the stability of Mpro.

Table S1 The optimized geometries and their energies are shown E_1=B3LYP and E_2= M05-2X methods using 6-31+G(d,p).

Name of the compounds	Optimized Geometries	B3LYP Energy (in a.u.)	M05-2X Energy (in a.u.)
NP-Hit 1		E_1 = -1757.0886	E_2 = -1756.9537
NP-Hit 2		E_1 = -1419.7228	E_2 = -1419.5942
NP-Hit 3		E_1 = -1202.8659	E_2 = -1202.7683
NP-Hit 4		E_1 = -1434.5949	E_2 = -1434.4357
Choline		E_1 = -328.7124	E_2 = -328.6541
Geranate		E_1 = -540.6271	E_2 = -540.5408
Ketoprofene		E_1 = -843.3461	E_2 = -843.2504
Linoleate		E_1 = -855.1525	E_2 = -855.0067

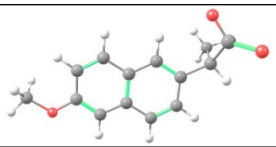
Naproxenate		E_1 = -767.1127	E_2 = -767.0205

Table S2 The ADMET properties of lopinavir.

ADME Properties	Lopinavir
MW	628.8
nHB acceptors	5
nHB donors	4
nRotB	17
nVio	1
TPSA (Å^2)	120
GI absorption	High
Hepatotoxicity	Inactive
Carcinogenicity	Inactive
PAINS	0

Table S3 The docking energies of Mpro with IL complexes are shown.

No. of Compounds	Compound Names	BEs (kcal/mol)
1.	Choline acesulfamate	-6.16
2.	Choline acetate	-7.26
3.	Choline alanine	-5.83
4.	Choline arginate	-5.25
5.	Choline aspartate	-7.55
6.	Choline bitartrate	-5.71
7.	Choline DBS	-6.50
8.	Choline DHP	-7.39
9.	Choline erucate	-8.08
10.	Choline geranate	-9.05
11.	Choline glutamate	-6.65
12.	Choline glycinate	-5.53
13.	Choline histidine	-5.84

14.	Choline hydroxide	-6.22
15.	Choline ketoprofene	-10.28
16.	Choline linoleate	-9.35
17.	Choline methionine	-5.88
18.	Choline myristate	-8.90
19.	Choline naproxenate	-10.76
20.	Choline oleate	-8.52
21.	Choline phenylacetate	-9.03
22.	Choline phenylalanine	-7.25
23.	Choline proline	-6.47
24.	Choline ricinoleate	-7.92
25.	Choline saccharine	-7.98
26.	Choline serine	-5.02
27.	Choline trichloroacetate	-6.88
28.	Choline tryptophan	-6.83
29.	Choline tyrosine	-6.72
30.	Choline valine	-4.95

Table S4 The average values of RMSD, RMSF and Rg of Mpro with natural compounds were shown.

Compounds	**$RMSD_{C\text{-}alpha}$ (Å)**	**RMSF (Å)**	**Rg (nm)**
Mpro	1.8599	1.4391	2.1927
Mpro- NP-Hit1	2.0443	1.1110	2.2033
Mpro- NP-Hit2	1.8862	1.1768	2.2133
Mpro- NP-Hit3	1.7743	1.2248	2.2112
Mpro- NP-Hit4	1.7837	1.3184	2.2144

Table S5 The average values of RMSD, RMSF and Rg of Mpro with ILs were shown.

Compounds	**$RMSD_{C\text{-}alpha}$ (Å)**	**RMSF (Å)**	**Rg (nm)**
Mpro	1.8599	1.4391	2.1927
Mpro-Naproxenate	1.5871	1.1379	2.1886
Mpro-Ketoprofene	1.2597	0.9960	2.1782
Mpro-Linoleate	1.8083	1.1140	2.1620
Mpro-Geranate	1.6406	1.1173	2.1959

Table S6 The average number of H-bonding interactions of Mpro with natural compounds and cholinium-based ILs.

Compound Names	**The average no. of H-bonds**
NP-Hit1	1.41 ± 0.01
NP-Hit2	1.28 ± 0.02
NP-Hit3	0.71 ± 0.01
NP-Hit4	2.49 ± 0.01
Choline naproxenate (3M)	46.35 ± 0.12
Choline ketoprofene (3M)	50.21 ± 0.12
Choline linoleate (3M)	39.46 ± 0.10
Choline geranate (3M)	41.31 ± 0.13

Table S7 The binding free energies were calculated for natural products with Mpro.[a]

Compound Names	**Ele**	**vdW**	**Pol**	**SASA**	**Average binding energy (in Kcal/mol)**
NP-Hit1	-39.12	-5.85	29.68	-3.94	-19.23 ± 3.99
NP-Hit2	-48.82	-7.04	34.99	-4.74	-25.62 ± 3.28
NP-Hit3	-43.61	-4.92	27.49	-4.25	-25.30 ± 3.45
NP-Hit4	-42.67	-7.41	30.05	-4.14	-24.19 ± 4.71

[a] Calculated MM-PBSA binding energies of cholinium-based ILs with Mpro of SARS-CoV-2. Ele = Electrostatic, vdW = van der Walls, Pol = Polar solvation and SASA = Solvent accessible surface area free energies are shown.

Table S8 The binding free energies were calculated for choline-based ILs with Mpro.[a]

Compound Names	Ele	vdW	Pol	SASA	Average binding energy (in Kcal/mol)
Choline naproxenate	-1025.34	-552.75	1304.03	-75.61	-346.67 ± 60.85
Choline ketoprofene	-1086.98	-704.95	1643.79	-93.37	-241.52 ± 60.27
Choline linoleate	-1173.53	-555.26	1496.49	-79.19	-311.49 ± 77.02
Choline geranate	-876.16	-520.10	1227.96	-75.90	-244.21 ± 72.88

[a] 3M concentration of cholinium-based ILs were used.

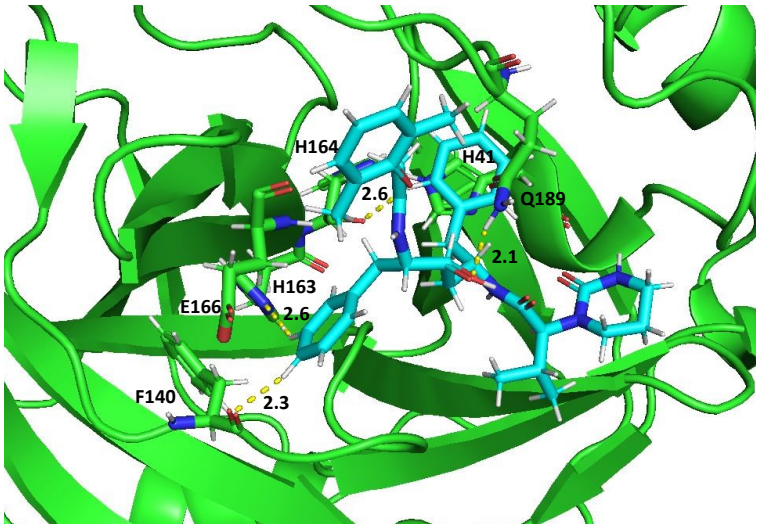


Fig. S1 The docking complexes of Mpro-lopinavir.

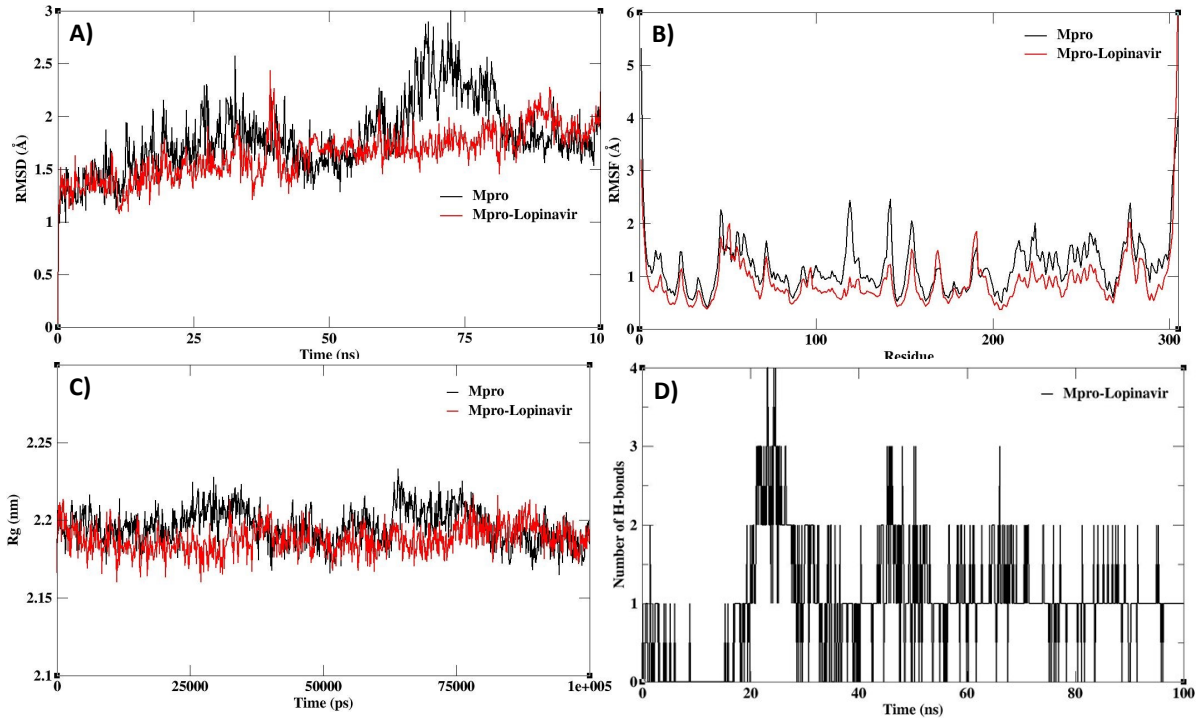


Fig. S2 The Mpro-lopinavir complex of A) RMSD B) RMSF C) Rg and D) H-bonding interactions are shown.

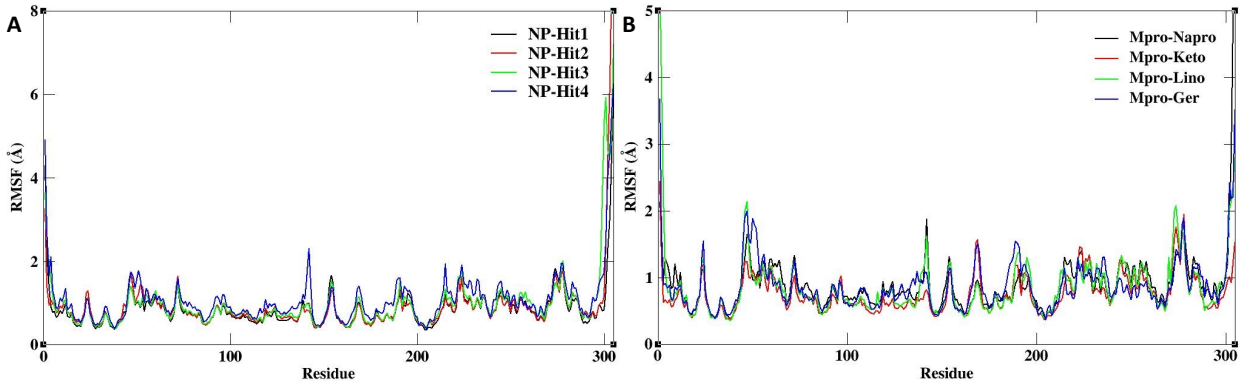


Fig. S3 RMSF plots of Mpro with A) Natural compounds and B) Choline-based ILs.

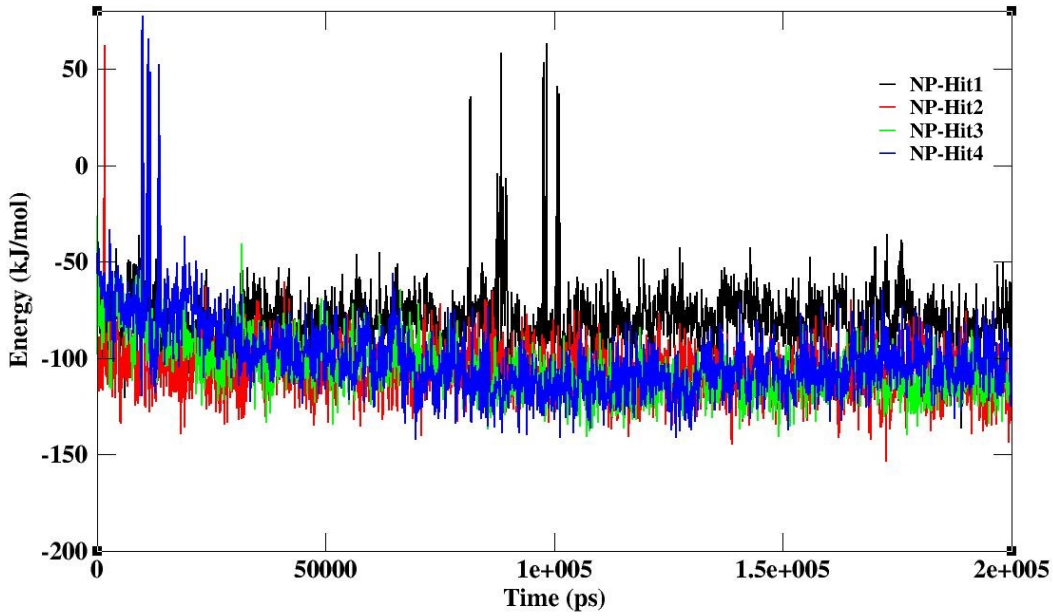


Fig. S4 The binding free energies of Mpro with natural compounds are shown.