Supplementary Information

Natural Compounds of Curcumin Against the Main Protease and Papain like Protease of SARS-CoV-2, a Possible Anti-COVID-19 Drug: Docking and Molecular Dynamics Simulation Studies

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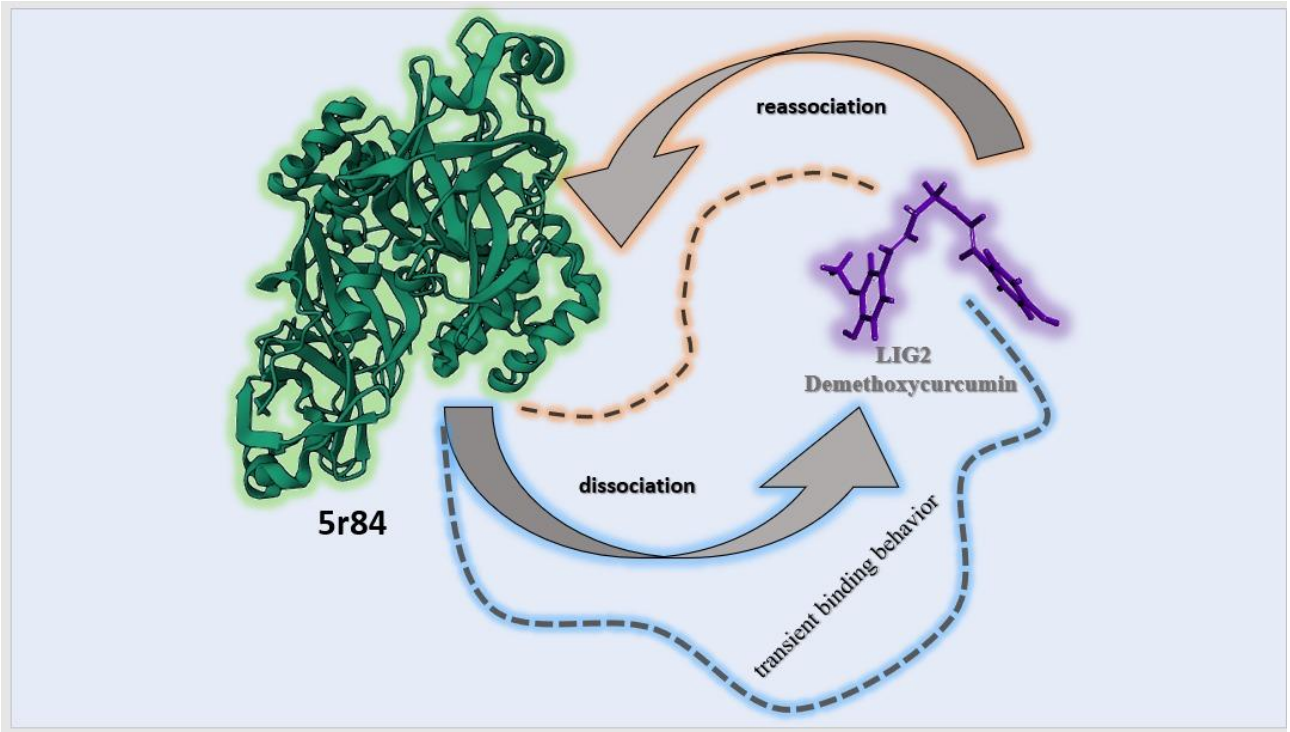

Figure S1. Molecular dynamics representation of the interaction between 3CLpro (PDB ID: 5R84) and demethoxycurcumin (LIG2). The diagram illustrates the dynamic binding process, highlighting ligand dissociation, transient binding states, and subsequent reassociation within the active site of the protease.

Table S1. Molecular docking analysis of ten natural curcumins against $3CL_{pro}$ using AutoDock 4.0 via MGTools 1.5.6

No.	CID	Name / ID	MF	Inhibition constant / μM	$\Delta G_{docking}$ / (kcal mol^{-1})	ΔE_{Int} / (kcal mol^{-1})	ΔG_{biding} / (kcal mol^{-1})
1	969516	curcumin	$C_{21}H_{20}O_6$	2.36	–13.36	–10.66	–7.68
2	5469424	demethoxycurcumin (LIG2)	$C_{20}H_{18}O_5$	0.253	–13.23	–11.68	–9.00
3	5315472	bisdemethoxycurcumin (LIG3)	$C_{19}H_{16}O_4$	0.841	–11.44	–10.67	–8.29
4	124072	tetrahydrocurcumin	$C_{21}H_{24}O_6$	35.93	–12.51	–9.64	–6.06
5	9906039	tetrahydrodemethoxycurcumin	$C_{20}H_{22}O_5$	1.66	–13.16	–11.17	–7.88
6	9796792	tetrahydrobisdemethoxycurcumin	$C_{19}H_{20}O_4$	2.06	–12.09	–10.74	–7.76
7	71315012	curcumin glucuronide	$C_{27}H_{28}O_{12}$	92.68	–16.34	–10.27	–5.50
8	10460395	cassumunin A (LIG8)	$C_{33}H_{34}O_8$	3.13	–14.82	–11.98	–7.51
9	10054109	cassumunin B (LIG9)	$C_{34}H_{36}O_9$	0.275	–18.52	–13.72	–8.95
10	5281767	curcumin_PE (LIG10)	$C_{21}H_{20}O_6$	6.55	–12.85	–10.05	–7.07

CID: compound identifier; MF: molecular formula; ΔG: Gibbs free energy change; ΔE: energy change.

Table S2. Ligand bond interaction with 5R84 protein

Ligand	Pi-Anion	Pi-sigma	Unfavorable donor-donor	π-π T-shaped	Hydrogen bond	Van der Waals	π-Sulfur	Carbon hydrogen	π-Donor hydrogen	Amide-π stacked	π-Alkyl	Alkyl
1					PHE140 ARG188	GLU166 ASN142	CYS145	HIS41	GLN189	LEU141 MET165	MET165	LEU141
2					LEU141 GLY143 HIS163	AG188		PHE140			CYS145 HIS41 MET49	
3			SER144	HIS41	TYR54, GLU166 LEU141,GLY143	GLN189	CYS44	MET165		ARG188	MET49 CYS145	
4	GLU166				ASN142.GLY143 SER144.CYS145 GLU166			GLU166		ARG188	MET165	
5				HIS41	TYR54 PHR140	AG188	CYS144			ASP187	MET49 CYS145	
6				HIS41	ASP187 GLU166, PHE140		MET165				MET49 CYS145	
7				HIS41	GLU166, GLN189 GLY143		MET49	MET49 ASP187				PRO52
8	GLU166	THR25			GLY143 HIS163 ARG188		MET49 CYS145	HIS172 GLN189			MRT165	LEU141 MET49
9	MET49			HIS41	HIS41 GLU166 ASN142 TYR54		MET49 CYS145				HIS41 HIS163 MET165	CYS145 MET165 LEU167

10	HIS41	HIS41	CY145	THR26	MET165	LEU27
		ASP187		TYR54		MET49
		GLU166				CYS44
						CYS145
						PRO52

Table S3. Molecular docking analysis of different compounds against PLPro (ID = 7nfv) using AutoDock 4.0 via MGTools 1.5.6

No.	CID	Name / ID	Inhibition constant / μM	$\Delta G_{docking}$ / (kcal mol^{-1})	ΔE_{Int} / (kcal mol^{-1})	ΔG_{biding} / (kcal mol^{-1})
1	969516	curcumin	74.03	–10.72	–8.62	–5.64
2	5469424	demethoxycurcumin	44.0	–9.57	–8.63	–5.94
3	5315472	bisdemethoxycurcumin	36.23	–9.16	–8.44	–6.06
4	124072	tetrahydrocurcumin	92.57	–11.41	–9.08	–5.50
5	9906039	tetrahydrodemethoxycurcumin	122.72	–10.49	–8.62	–5.34
6	9796792	tetrahydrobisdemethoxycurcumin	101.40	–9.31	–8.43	–5.45
7	92024088	curcumin glucuronide	29.56	–16.36	–10.95	–6.18
8	10460395	cassumunin A	11.84	–14.69	–11.20	–6.72
9	10054109	cassumunin B	12.94	–15.35	–11.44	–6.67
10	5281767	curcumin PE	25.75	–11.08	–9.24	–6.26

CID: compound identifier; MF: molecular formula; ΔG: Gibbs free energy change; ΔE: energy change.

Table S4. Ligand bond interaction with 7nfv protein

Ligand	Pi-sigma	π-π T-Stacked	Unfavorable donor-donor(a)/acceptor-aceptor(b)	π-π T-shaped	Conventional hydrogen bonds	Van der Waals	π-Sulfur	Carbon hydrogen bond	π-Donor hydrogen bond	Amide-π stacked	π-Alkyl	Alkyl
1				TRP106	ASN109			ASP286 GLY587			ALA288 LEU289 TRP106	CYS111 HYS272
2			LEU289(a) ASN267(a)	TRP106	CYS270 ASP286		CYS270	TRP106			LEU289	
3			ASP286(b) ALA288(a)		GLY271 ASN109		CYS270		HIS272		ALA288 LEU289	
4	LEU289		ALA288(a)				CYS270	ASP286			HIS272 TRP106	CY111
5	TRP106 LEU289		ALA288(a)		ASN109			HIS272 GLY287 ASP286	HIS272		HIS272 TRP106 ALA288	
6			ALA288(a)	TRP106	GLY171 TRP106		CYS270				ALA280 LEU289	
7			ALA288(a)	TRP106 HIS272	TRP106, ASP286 ALA288	CYS270		CYS270 GLY266 LYS105			TRP106	
8				HIS272	ASP286		CYS270	GLY266	ASN109		CYS270 LEU162 HIS272	CYS270 LEU162 LEU289
9		HIS272		TRP106	ASP28			CYS270			CYS270 ALA288 LEU289 HIS272	CYS270 LEU289
10				TRP106	HIS272, ASN109 ASP286		CYS111	TRP106			ALA278 LEU289	CYS270