Supplementary Tables

Antiviral phytochemicals identified in *Rhododendron arboreum* petals exhibited strong binding to SARS-CoV-2 M^{Pro} and Human ACE2 receptor

Maneesh Lingwan[a#], Shagun Shagun[a#], Yogesh Pant[a], Bandna Kumari[a], Ranjan K Nanda[b], Shyam K Masakapalli[a*]

a) BioX Center, School of Basic Sciences, Indian Institute of Technology Mandi, Kamand 175075, Himachal Pradesh, India

b) Translational Health Group, International Centre for Genetic Engineering and Biotechnology, New Delhi 110067, India

# Joint first authors/ Equal contribution

Supplementary	Description
Table S1	Secondary metabolites of *R. arboreum* petals. A) Hot water extracts analysed using GC-MS. The retention time (RT), m/z product ion, and their match scores against the NIST17 and Fiehn13 library are presented. The area of the peaks among all the replicates are listed below (n=4). B) Secondary metabolites reported by Shrestha et al., 2016 using LC-MS.
Table S2	Assessment of ADME (absorption, distribution, metabolism and elimination) properties of *R. arboreum* phytochemicals for drug discovery and development.
Table S3	Structural information of SARS-CoV-2 Main protease (6LU7) and ACE2 host cell receptor (1R4L) along with their native ligands. Active sites of the target proteins were analysed by using Computed Atlas for Surface Topography of Proteins (CASTp). The amino acids residues found in the active sites pockets of SARS-CoV-2 Main protease (6LU7) and ACE2 host cell receptor (1R4L) are tabulated.
Table S4	Blind docking of the secondary metabolites identified in *R. arboreum* petals against target protein-SARS-CoV-2 Mpro (6LU7) and Human Angiotensin Converting Enzyme (1R4L). Glycyrrhizic acid was taken as a positive control.
Table S5	*Rhododendron arboreum* petal phytochemicals with reported anti-viral studies

Table S1. Secondary metabolites of R. arboreum petals. A) Hot water extracts analysed using GC-MS. The retention time (RT), m/z product ion, and their match scores against the NIST17 and Fiehn13 library are presented. The area of the peaks among all the replicates are listed below (n=4). B) Secondary metabolites reported by Shrestha 2016 using LC-MS.

A								
Sl.No	**Metabolite**	**RT**	**Product Ion (m/z)**	**Match Factor**	**% Peak Area Replicate 1**	**% Peak Area Replicate 2**	**% Peak Area Replicate 3**	**% Peak Area Replicate 4**
1	3-Hydroxybenzoic acid	15.88	267	71.66	0.006	0.011	0.006	0.010
2	Shikimic acid	18.31	204	95.19	2.804	1.219	3.072	1.015
3	Protocatechuic acid	18.49	370	88.97	0.085	0.071	0.052	0.094
4	Quinic acid	19.5	345	91.04	12.028	6.517	8.291	5.559
5	Coumaric acid	20.86	293	88.69	0.056	0.058	0.062	0.048
6	Caffeic acid	27.00	396	70.41	0.013	0.018	0.016	0.016
7	Epicatechin	42.68	368	90.13	2.839	1.933	3.997	2.092
8	Catechin	42.98	368	79.33	2.830	1.930	3.997	2.097
9	5-O-Coumaroyl-D-quinic acid	44.40	345	97.41	1.137	0.513	0.764	0.778
10	3-Caffeoyl-quinic acid	44.70	345	93.87	1.113	10.790	0.764	0.783
11	2,4-Quinolinediamine	45.50	370	71.31	0.009	0.005	0.020	0.010
12	5-O-Feruloylquinic acid	46.35	345	75.82	14.215	10.869	14.348	10.107
	Others - Sugars, Organic acids, Aminoacids …etc	variable	variable	variable	62.87	66.07	64.61	77.39

B		
Sl. No.	**Metabolite**	**Mass**
13	Epicatechin gallate	441.0827
14	Quercetin	301.0354
15	Quercetin-O-pentoside	433.0776
16	Quercetin-O-rhamnoside	447.0933
17	Kaempferol-O-pentoside	417.0827
18	Kaempferol	286.23

Reference:
Shrestha, A. (2016). Phytochemical Analysis of Rhododendron Species (Doctoral dissertation, IRC-Library, Information Resource Center der Jacobs University Bremen).

Table S2. Assessment of ADME (absorption, distribution, metabolism and elimination) properties of R. arboreum phytochemicals for drug discovery and development.

Pubchem CID	14207924	7420	637542	9799386	689043	9064	1794427	72276	72	8742	6441280	6508	107905	5280863	14749097	5280343	5878729	5280459
Molecules	2,4-Quinoline diamine	3-Hydroxy benzoic acid	4-Coumaric acid	5-O-Feruloyl quinic acid	Caffeic acid	Catechin	3-Caffeoyl-quinic acid	Epicatechin	Proto catechuic acid	Shikimic acid	5-O-Coumaroyl-D-quinic acid	Quinic acid	Epicatechin gallate	Kaempferol	Kaempferol-O-pentoside	Quercetin	Quercetin-O-pentoside	Quercetin-O-rhamnoside
Canonical SMILES	Nc1cc(N)c2c(n1)cccc2	Oc1cccc(c1)C(=O)O	OC(=O)C=Cc1ccc(cc1)O	COc1cc(C=CC(=O)OC2CC(O)(CC(C2O)O)C(=O)O)ccc1O	OC(=O)C=Cc1ccc(c(c1)O)O	Oc1cc2OC(c3ccc(c(c3)O)O)C(Cc2c(c1)O)O	O=C(OC1CC(O)(CC(C1O)O)C(=O)O)C=Cc1ccc(c(c1)O)O	Oc1cc2OC(c3ccc(c(c3)O)O)C(Cc2c(c1)O)O	O=C(c1ccc(c(c1)O[Si](C)(C)C)O[Si](C)(C)C)O[Si](C)(C)C	OC1CC(=CC(C1O)O)C(=O)O	O=C(OC1CC(O)(CC(C1O)O)C(=O)O)C=Cc1ccc(cc1)O	OC1C(O)CC(CC1O)(O)C(=O)O	Oc1cc(O)c2c(c1)OC(C(C2)OC(=O)c1cc(O)c(c(c1)O)O)c1ccc(c(c1)O)O)O	Oc1ccc(cc1)c1oc2cc(O)cc(c2c(=O)c1O)O	Oc1ccc(cc1)c1oc2cc(O)cc(c2c(=O)c1OC1OCC(C(C1O)O)O)O	Oc1cc(O)c2c(c1)oc(c(c2=O)O)c1ccc(c(c1)O)O	Oc1cc(O)c2c(c1)oc(c(c2=O)OC1OCC(C(C1O)O)O)c1ccc(c(c1)O)O	Oc1cc(O)c2c(c1)oc(c(c2=O)OC1OC(C)C(C(C1O)O)O)c1ccc(c(c1)O)O
Formula	C9H9N3	C7H6O3	C9H8O3	C17H20O9	C9H8O4	C15H14O6	C16H18O9	C15H14O6	C16H30O4Si3	C7H10O5	C16H18O8	C7H12O6	C22H18O10	C15H10O6	C20H18O10	C15H10O7	C20H18O11	C21H20O11
MW	159.19	138.12	164.16	368.34	180.16	290.27	354.31	290.27	370.66	174.15	338.31	192.17	442.37	286.24	418.35	302.24	434.35	448.38
#Heavy atoms	12	10	12	26	13	21	25	21	23	12	24	13	32	21	30	22	31	32
#Aromatic heavy atoms	10	6	6	6	6	12	6	12	6	0	6	0	18	16	16	16	16	16
Fraction Csp3	0	0	0	0.41	0	0.2	0.38	0.2	0.56	0.57	0.38	0.86	0.14	0	0.25	0	0.25	0.29
#Rotatable bonds	0	1	2	6	2	1	5	1	7	1	5	1	4	1	3	1	3	3
#H-bond acceptors	1	3	3	9	4	6	9	6	4	5	8	6	10	6	10	7	11	11
#H-bond donors	2	2	2	5	3	5	6	5	0	4	5	5	7	4	6	5	7	7
MR	50.55	35.42	45.13	87.97	47.16	74.33	83.5	74.33	103.15	38.43	81.48	40.11	110.04	76.01	102.17	78.03	104.19	109
TPSA	64.93	57.53	57.53	153.75	77.76	110.38	164.75	110.38	44.76	97.99	144.52	118.22	177.14	111.13	170.05	131.36	190.28	190.28
iLOGP	1.1	0.86	0.95	1.47	0.97	1.47	0.96	1.47	4.72	0.62	1.08	-0.12	1.31	1.7	1.21	1.63	1.61	1.27
XLOGP3	1.16	1.5	1.46	-0.1	1.15	0.36	-0.42	0.36	5.99	-1.72	-0.07	-2.37	1.53	1.9	0.78	1.54	0.43	0.86
WLOGP	1.42	1.09	1.38	-0.45	1.09	1.22	-0.75	1.22	5.11	-1.52	-0.46	-2.32	2.2	2.28	0.39	1.99	0.1	0.49
MLOGP	0.98	0.99	1.28	-0.81	0.7	0.24	-1.05	0.24	2.97	-1.43	-0.54	-2.14	0.05	-0.03	-1.57	-0.56	-2.06	-1.84
Silicos-IT Log P	1	0.74	1.22	-0.07	0.75	0.98	-0.61	0.98	-0.22	-1.36	-0.15	-1.82	1.04	2.03	0.38	1.54	-0.1	0.01
Consensus Log P	1.13	1.03	1.26	0.01	0.93	0.85	-0.38	0.85	3.72	-1.08	-0.03	-1.75	1.23	1.58	0.24	1.23	0	0.16

ESOL Log S	-2.17	-2.02	-2.02	-1.84	-1.89	-2.22	-1.62	-2.22	-5.64	0.23	-1.75	0.53	-3.7	-3.31	-3.12	-3.16	-2.99	-3.33
ESOL Solubility (mg/ml)	1.07	1.32	1.58	5.38	2.32	1.74	8.5	1.74	0.000844	296	6.04	648	0.0885	0.14	0.316	0.211	0.447	0.208
ESOL Solubility (mol/l)	0.00669	0.00956	0.00965	0.0146	0.0129	0.00598	0.024	0.00598	0.00000228	1.7	0.0178	3.37	0.0002	0.00049	0.000755	0.000698	0.00103	0.000464
ESOL Class	Soluble	Soluble	Soluble	Very soluble	Very soluble	Soluble	Very soluble	Soluble	Moderately soluble	Highly soluble	Very soluble	Highly soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble
Ali Log S	-2.12	-2.32	-2.27	-2.68	-2.38	-2.24	-2.58	-2.24	-6.71	0.18	-2.51	0.43	-4.86	-3.86	-3.93	-3.91	-3.99	-4.44
Ali Solubility (mg/ml)	1.21	0.667	0.873	0.776	0.755	1.66	0.942	1.66	0.0000728	261	1.04	512	0.00612	0.0398	0.049	0.0374	0.0441	0.0163
Ali Solubility (mol/l)	0.00761	0.00483	0.00532	0.00211	0.00419	0.00572	0.00266	0.00572	0.000000196	1.5	0.00307	2.66	0.0000138	0.000139	0.000117	0.000124	0.000102	0.0000363
Ali Class	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Poorly soluble	Highly soluble	Soluble	Highly soluble	Moderately soluble	Soluble	Soluble	Soluble	Soluble	Moderately soluble
Silicos-IT LogSw	-2.97	-1.17	-1.28	-0.29	-0.71	-2.14	0.4	-2.14	-5.31	1.75	-0.18	2.08	-3.09	-3.82	-2.53	-3.24	-1.94	-2.08
Silicos-IT Solubility (mg/ml)	0.171	9.4	8.67	189	35.1	2.09	894	2.09	0.00182	9750	222	23000	0.36	0.0429	1.23	0.173	4.96	3.69
Silicos-IT Solubility (mol/l)	0.00107	0.0681	0.0528	0.513	0.195	0.00719	2.52	0.00719	0.0000049	56	0.656	120	0.000815	0.00015	0.00294	0.000573	0.0114	0.00822
Silicos-IT class	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Moderately soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble
GI absorption	High	High	High	Low	High	High	Low	High	High	High	Low	Low	Low	High	Low	High	Low	Low
BBB permeant	Yes	Yes	Yes	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No
Pgp substrate	No	No	No	No	No	Yes	No	Yes	Yes	No	No	Yes	No	No	No	No	No	No
CYP1A2 inhibitor	Yes	No	No	No	No	No	No	No	Yes	No	No	No	No	Yes	No	Yes	No	No
CYP2C19 inhibitor	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
CYP2C9 inhibitor	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No

CYP2D6 inhibitor	No	No	No	No	No	No	No	No	Yes	No	No	No	No	Yes	No	Yes	No	No
CYP3A4 inhibitor	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	Yes	No	No
log Kp (cm/s)	-6.45	-6.08	-6.26	-8.62	-6.58	-7.82	-8.76	-7.82	-4.31	-8.58	-8.41	-9.15	-7.91	-6.7	-8.3	-7.05	-8.64	-8.42
Lipinski #violations	0	0	0	0	0	0	1	0	0	0	0	0	1	0	1	0	2	2
Ghose #violations	1	3	0	1	0	0	1	0	0	2	1	1	0	0	0	0	0	0
Veber #violations	0	0	0	1	0	0	1	0	0	0	1	0	1	0	1	0	1	1
Egan #violations	0	0	0	1	0	0	1	0	0	0	1	0	1	0	1	0	1	1
Muegge #violations	1	1	1	1	1	0	2	0	1	1	0	2	2	0	2	0	3	3
Bioavailability Score	0.55	0.56	0.56	0.11	0.56	0.55	0.11	0.55	0.55	0.56	0.56	0.56	0.55	0.55	0.55	0.55	0.17	0.17
PAINS #alerts	0	0	0	0	1	1	1	1	0	0	0	0	1	0	0	1	1	1
Brenk #alerts	0	0	1	1	2	1	2	1	1	0	1	0	1	0	0	1	1	1
Leadlikeness #violations	1	1	1	1	1	0	1	0	2	1	0	1	1	0	1	0	1	1
Synthetic Accessibility	1.7	1	1.61	4.25	1.81	3.5	4.16	3.5	3.97	3.77	4.07	3.34	4.16	3.14	5.02	3.23	5.05	5.28

Remarks*		
A	**Aqueous solubility is expressed on the basis of log S scale value ranges between -10 and 0 which is given in table mentioned below**	
	Log S value	Aqueous solubility
	<-10	Insoluble
	-10 to -6	Poorly soluble
	-6 to -4	Moderately soluble

	-4 to -2	soluble
	-2 to 0	Very soluble
	>0	Highly soluble
B	**SwissADME have five methods to calculate the lipophilicity of molecules, and explained in**	
1	Log Po/w (the partition coefficient between octanol and water which shows lipophilicity of molecules	
2	iLOGP is in-house physics-based method in which Generalized-Born and solvent accessible surface area model is used to calculate the free energy of solvation in n-octanol and water.	
3	XLOGP3 is an atomistic method comprising the corrective factors and knowledge-based library.	
4	WLOGP is a purely atomistic method based on the fragmental system.	
5	MLOGP is a prototype of topological method based on a linear relationship with 13 molecular descriptors	
	*SILICOS-IT is hybrid methods which rely on 7 topological descriptors and 27 fragments. Arithmetic mean of the values of the 5 methods is calculated in consensus log Po/w	

Table S3. Structural information of SARS-CoV-2 Main protease (6LU7) and ACE2 host cell receptor (1R4L) along with their native ligands. Active sites of the target proteins were analysed by using Computed Atlas for Surface Topography of Proteins (CASTp). The amino acids residues found in the active sites pockets of SARS CoV-2 Main protease (6LU7) and ACE2 host cell receptor (1R4L) are tabulated.

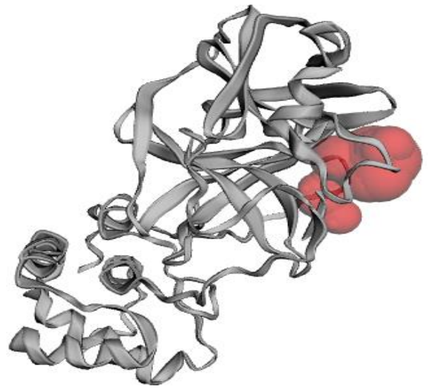
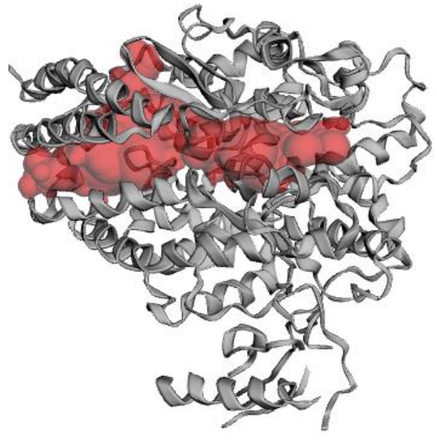
Target proteins	PDB ID	Structure	Native ligands	Active Sites	Active site amino acids
SARS-CoV-2 Main protease	6LU7		N-[(5-Methylisoxazol-3-Yl) Carbonyl] Alanyl-L-Valyl-N~1~-((1r,2z)-4-(Benzyloxy)-4-Oxo-1-{[(3r)-2-Oxopyrrolidin-3-Yl]Methyl}But-2-Enyl)-L-Leucinamide		THRA:24, THRA:25, THRA:26, GLYA:143, LEUA:27, THRA:45, SERA:46, CYSA:145, HISA:164, ASPA:187, HISA:41, ARGA:188, META:49, GLNA:189, GLUA:166, THRA:190, ALAA:191, PROA:168, PHEA:140, LEUA:141, GLNA:192, HISA:172, HISA:163, ASNA:142, META:165, SERA:144, VALC:3, LEUC:4
Human Angiotensin Converting Enzyme	1R4L		N-Acetyl-D-Glucosamine Zinc Ion Chloride Ion (S,S)-2-{1-Carboxy-2-[3-(3,5-Dichloro-Benzyl)-3h-Imidazol-4-Yl]-Ethylamino}-4-Methyl-Pentanoic Acid		PHEA:32, GLUA:37, PHEA:40, SERA:43, SERA:44, SERA:47, TYRA:50, ASNA:52, ILEA:54, META:62, ASNA:63, GLYA:66, ASPA:67, TRPA:69, SERA:70, ALAA:71, LEUA:73, LYSA:74, SERA:77, LEUA:91, THRA:92, LYSA:94, LEUA:95, GLNA:96, GLNA:98, ALAA:99, LEUA:100, GLNA:102, ASNA:103, GLYA:104, SERA:105, SERA:106, LEUA:108, GLUA:110, SERA:113, LYSA:114, LEUA:116, ASNA:117, LEUA:120, ASNA:121, SERA:124, TYRA:127, SERA:128, THRA:129, GLYA:130, LYSA:131, CYSA:141, LEUA:142, LEUA:143, LEUA:144, GLUA:145, PROA:146, ASNA:149, GLUA:150, META:152, ALAA:153, ASNA:154, LYSA:187, META:190, ALAA:191, ASNA:194, TYRA:196, TYRA:199, TYRA:202, TRPA:203, GLYA:205, ASPA:206, GLUA:208, VALA:209, ASNA:210, GLYA:211, VALA:212, GLYA:268, ASPA:269, META:270, TRPA:271, ARGA:273, PHEA:274, THRA:276, ASNA:277, ILEA: 291, ASPA:292, THRA:294, ASPA:335, GLYA:337, ASNA:338, VALA:339, GLNA:340, LYSA:341, ALAA:342, VALA:343, CYSA:344, HISA:345, PROA:346, THRA:347, ALAA:348, TRPA:349, ASPA:350, GLYA:352, LYSA:353, GLYA:354, PHEA:356, LEUA:359, META:360, CYSA:361, LYSA:363, THRA:365, META:366, ASPA:367, ASPA:368, LEUA:370, THRA:371, HISA:374, GLUA:375, HISA:378, ASPA:382, TYRA:385, ALAA:386, PHEA:390, LEUA:391, LEUA:392, ARGA:393, ASNA:394, GLYA:395, ALAA:396, ASNA:397, GLUAA:398, HISA:401, GLUA:402, GLUA:406, SERA:409, LEUA:410, ALAA:413, PHEA:438, LYSA:441, GLNA:442, THRA:445, ILEA:446, THRA:449, LEUA:503, PHEA:504, HISA:505, SERA:507, ASNA:508, ASPA:509, TYRA:510, SERA:511, ARGA:514, TYRA:515, ARGA:518, THRA:519, GLNA:522, LYSA:562, SERA:563, GLUA:564, PROA:565, TRPA:566

Table S4. Blind docking of the secondary metabolites identified in *R. arboreum* petals against Target protein- SARS-CoV-2 Mpro (6LU7) and Human Angiotensin Converting Enzyme (1R4L). Glycyrrhizic acid was taken as a positive control

Pubchem CID	Phytochemicals	Target protein-SARS-CoV-2 Mpro (6LU7)		Human Angiotensin Converting Enzyme (1R4L)	
		Binding affinity (Kcal/mol)	Amino acid Residues	Binding affinity (Kcal/mol)	Amino acid Residues
14982	Glycyrrhizic acid (Positive control) (Zhang et al., 2020)	-8	ASNA:151, SERA:158, VALA:104, ILEA:106, ARGA:105, GNA:107, THRA:111, ASPA:245, THRA:243, GLYA:108, THRA:292, HISA:246, VALA:202, ILEA:249, PHEA:294, PROA:293, GLNA:110	-10.5	ASPA:206, ARGA:514, GLUA:402, HISA:378, TYRA:202, LYSA:562, HISA:401, ASNA:394, GLUA:398, TYRA:510, ASPA:508, TRPA:206, ASNA:394, ASPA:206, TYRA:385, ASPA:350, PHEA:390, TRPA:69, PHEA:40, LEUA:391, LEUA:73, ALAA:99, PHEA:92
14207924	2,4-Quinolinediamine	-5.3	LEUA:286, ASPA:289, LEUA:287, THRA:199, TYRA:239, TYRA:237, LEUA:272, META:276	-6.3	ALAA:348, TRPA:349, THRA:347, HISA:378, GLUA:402, TYRA:515, HISA:505, HISA:345, PROA:346, PHEA:504, TYRA:510
7420	3-Hydroxybenzoic acid	-5.4	PHEA:294, THRA:111, THRA:292, GLNA:110, ASPA:295, ASNA:151, GLNA:127, PHEA:112, PHEA:8, ASA:153, ILEA:152	-5.8	ARGA:273, HISA:345, TYRA:515, HISA:505, HISA:378, GLUA:402, ARGA:514, PHEA:504, TYRA:510, THRA:347, PROA:346, THRA:371, GLUA:375, HISA:374
637542	4-Coumaric acid	-5.9	ASPA:153, LYSA:102, SERA:158, VALA:104, ASNA:151, GLNA:110, THRA:111, THRA:292, ASPA:295, PHEA:294	-6.2	PROA:346, HISA:345, TYRA:515, ARGA:273, HISA:505, THRA:371, PHEA:274, ASPA:367, THRA:276, THRA:445

9799386	5-O-Feruloylquinic acid	-7.1	THRA:24, THRA:25, LEUA:27, HISA:41, META:49, PHEA:140, LEUA:141, ASNA:142, GLYA:143, SERA:144, CYSA:145, GLUA:166, META:165, HISA:163, HISA:164, HISA:172, GLNA:189,	-8.4	ASPA:367, ASPA:368, THRA:371, ARGA:273, GLUA:375, ALAA:348, HISA:374, THRA:347, HISA:378, ARGA:514, GLUA:402, TYRA:510, HISA:505, PHEA:504, TYRA:515, HISA:345, PHEA:274 META:360, PROA:346,
689043	Caffeic acid	-5.8	ASPA:153, LYSA:102, SERA:158, VALA:104, ASNA:151, GLNA:110, THRA:111, THRA:292, ASPA:295, PHEA:294	-6.4	PHEA:274, THRA:449, ILEA:446, THRA:519, GLNA:522, ARGA:518, THRA:445, GLUA:406, LEUA:370, ASPA:367, THRA:371
9064	Catechin	-6.7	THRA:24, THRA:25, LEUA:27, HISA:41, META:49, PHEA:140, LEUA:141, ASNA:142, GLYA:143, SERA:144, CYSA:145, GLUA:166, META:165, HISA:163, HISA:172	-9.2	THRA:445, ARGA:518, GLUA:406, ARGA:273, TYRA:515, GLUA:402, HISA:378, HISA:505, THRA:347, PHEA:504, HISA:345, GLUA:375, HISA:374, THRA:371, PROA:346, ASPA:269, THRA:276, ASPA:367, PHEA:274,
1794427	3-Caffeoyl-quinic acid	-7	LEUA:271, GLYA:275, THRA:199, META:276, THRA:198, ASPA:197, LYSA:137, ASPA:289, GLUA:290, ARGA:131, LEUA:286, TYRA:239, VALA:204, LEUA:287, LEUA:272, TYRA:237	-8.5	SERA:44, PHEA:40, LEUA:351, ASPA:350, THRA:347, ALAA:348, GLUA:375, PROA:346, HISA:378, HISA:374, HISA:345, PHEA:504, GLUA:402, HISA:505, TYRA:515, SERA:511, TYRA:510, ARGA:514, TRPA:349, SERA:47

72276	Epicatechin	-7.1	TYRA:237, TYRA:239, THRA:199, THRA:198, ARGA:131, ASPA:197, LYSA:137, ASPA:289, LEUA:286, VALA:204, LEUA:287, LEUA:272	-8.4	THRA:445, LEUA:370, ARGA:518, GLUA:406, ARGA:273, TYRA:515, GLUA:402, HISA:378, HISA:505, THRA:347, HISA:345, GLUA:375, THRA:371, PROA:346, THRA:276, PHEA:274, ASPA:367, HISA:374
72	Protocatechuic acid	-5.4	PHEA:140, LEUA:141, SERA:144, GLYA:143, ASNA:142, CYSA:145, GLNA:189, GLUA:166, META:165, HISA:163	-5.8	ALAA:348, TRPA:349, THRA:347, HISA:378, GLUA:402, TYRA:515. HISA:505, GLUA:375, HISA:374, HISA:345, PROA:346, PHEA:504, TYRA:510
8742	Shikimic acid	-5.3	PHEA:140, LEUA:141, SERA:144, GLYA:143, ASNA:142, CYSA:145, GLUA:166, META:165, HISA:163, HISA:164, HISA:172,	-6.1	ALAA:348, THRA:347, HISA:378, GLUA:402, TYRA:515, HISA:505, HISA:374, GLUA:375, HISA:345, PROA:346, PHEA:504, TYRA:510,
6441280	5-O-Coumaroyl-D-quinic acid	-7.2	THRA:25, THRA:26, LEUA:27, HISA:41, META:49, PHEA:140, LEUA:141, ASNA:142, GLYA:143, SERA:144, CYSA:145, GLUA:166, META:165, HISA:163, HISA:164 HISA:172, GLNA:189	-8.3	ASPA:367, THRA:371, GLUA:375, GLUA:402, HISA:378, ARGA:514, ALAA:348, THRA:347, TYRA:510, PHEA:504, TYRA:515, HISA:505, HISA:345, ARGA:273, HISA:374, PROA:346, PHEA:274

6508	Quinic acid	-5.6	ASNA:72, SERA:121, ASNA:119, GLYA:120, VALA:18, ALAA:70, GLNA:69, GLYA:71, GLNA:19	-6.6	HISA:374, GLUA:375, HISA:345, HISA:505, PHEA:504, TYRA:515, TYRA:510, GLUA:402, TRPA:349, ALAA:348 ARGA:514, THRA:347, HISA:378, PROA:346
5280343	Quercetin	-7	THRA:24, THRA:25, THRA:26, LEUA:27, HISA:41, PHEA:140, LEUA:141, ASNA:142, GLYA:143, SERA:144, CYSA:145, GLUA:166, META:165, HISA:163, HISA:172	-9.3	LEUA:370, GLUA:406, ARGA:518, GLUA:402, HISA:505, TYRA:515, HISA:378, THRA:347, PROA:346, HISA:345, GLUA:375, HISA:374, THRA:371, PHEA:274, ARGA:273, ASPA:269, THRA:276, ASPA:367, THRA:445
5878729	Quercetin-O-pentoside	-7.9	LYSA:137, ARGA:131, ASNA:238, THRA:198, THRA:199, ASPA:197, LEUA:272, TYRA:239, LEUA:287, LEUA:286, ASPA:289, GLUA:288, LYSA:5, GLUA:290	-9.8	GLUA:406, ARGA:518, THRA:347, GLUA:375, HISA:378, TYRA:515, HISA:505, GLUA:402, HISA:374, THRA:371, ARGA:273, LEUA:503, TRPA:271. HISA:345, PHEA:274, PROA:346, THRA:276, ASPA:367, LEUA:370, THRA:445
14749097	Kaempferol-O-pentoside	-7.8	LEUA:272, TYRA:239, THRA:199, ASPA:197, THRA:198, ASNA:238, LYSA:137, ARGA:131, GLUA:290, LYSA:5, GLUA:288, ASPA:289, LEUA:286, LEUA:287	-9.6	PHEA:274, ASPA:367, THRA:276, THRA:445, GLUA:406, PROA:346, ARGA:518, GLUA:375, THRA:347, TYRA:515, HISA:505, GLUA:402, HISA:378, HISA:374, ARGA:273, HISA:345, THRA:371

5280863	Kaempferol	-7	THRA:25, THRA:26, LEUA:27, HISA:41, PHEA:140, LEUA:141, ASNA:142, GLYA:143, SERA:144, CYSA:145, GLUA:166, META:165, HISA:163, HISA:172, GLNA:189	-8.6	HISA:505, HISA:345, ARGA:273, TYRA:515, HISA:378, GLUA:375, GLUA:402, ARGA:518, HISA:374, PHEA:274, GLUA:406, THRA:445, SERA:409, LEUA:370, THRA:371, PROA:346
107905	Epicatechin gallate	-7.4	ASPA:197, ASNA:238, TYRA:237, THRA:199, THRA:198, LYSA:137, ASPA:289, ARGA:131, LEUA:286, LEUA:287, META:276, ALAA:285, GLYA:275, LEUA:271, LEUA:272, TYRA:239	-9.1	TYRA:515, HISA:345, HISA:505, PHEA:504, TYRA:510, THRA:347, TRPA:349, SERA:44, SERA: 44, ASPA:350, ALAA:348, ILEA:379, ASPA:382, TYRA:385, HISA:401, HISA:378, ARGA:514, GLUA:375, HISA:374, GLUA:402, THRA:371, PROA:346,
5280459	Quercetin-O-rhamnoside	-7.7	LEUA:272, TYRA:239, THRA:199, ASPA:197, THRA:198, ASNA:238, LYSA:137, ARGA:131, GLUA:290, LYSA:5, GLUA:288, ASPA:289, LEUA:286, LEUA:287	-10	THRA:445, ASPA:367, HISA:374, THRA:371, HISA:505, TYRA:515, GLUA:375, PROA:346, HISA:345, ARGA:273, LEUA:144, ASNA:149 TRPA:271, ASPA:269, PHEA:274, GLUA:406, ARGA:518

Table S5. *Rhododendron arboreum* petal phytochemicals with reported anti-viral studies

Phytochemicals	Antiviral Activity		References
4-Coumaric acid	Anti-human rhinoviruses	In vitro study	Kwon et al., 2019,
	Anti-influenza virus A (H3N2) and human herpes virus 1 and 2 (HSV-1 and HSV-2)	In vitro study	Stankova et al., 2009
Caffeic acid	Anti-hepatitis B virus	In vivo and in vitro study	Wang et al., 2009
	Anti-herpes simplex virus type 1 (HSV-1)	In vitro study	Ikeda et al, 2011
	Anti-severe fever with thrombocytopenia syndrome virus (SFTSV)	In vitro study	Ogawa et al., 2018
Catechin	Anti-influenza	In vitro study	Song et al., 2005
	Anti-hepatitis B virus	In vivo study	Li et al., 2001
	Anti-herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2)	In vitro study	Lyu et al., 2005
3-Caffeoyl-quinic acid	Anti-hepatitis B virus	In vivo and in vitro study	Wang et al., 2009
	Anti-influenza virus (H1N1)	In vitro study	Urushisaki et al., 2011
	Anti-HIV activity	Molecular docking study	Serina et al., 2017
	Anti-avian influenza virus (H5N1)	Molecular docking study	Ren et al., 2019
	Anti-influenza A (H1N1/H3N2)	In vivo and in vitro study	Ding et al., 2017
	Anti-enterovirus 71	In vitro study	Li et al., 2013
	Anti-herpes virus	In vitro study	Xiehuang et al., 2008
Epicatechin	Anti-mayaro virus	In vitro and molecular docking study	Ferreira et al., 2018
	Anti-herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2)	In vitro study	Lyu et al., 2005
Protocatechuic acid	Anti-avian influenza virus H9N2	In vivo study	Ou et al., 2014
	Anti-hepatitis B virus	In vitro study	Dai et al., 2017
	Anti-influenza virus A	In vitro study	Lu et al., 2002

	Anti-herpes simplex virus	In vitro study	Hassan et a., 2017
Shikimic acid	Anti-avian influenza virus	In vitro study	Singh et al., 2020
	Precursor molecule for the drug oseltamivir phosphate used against influenza viruses types A and B, avian influenza virus H5N1, and human influenza virus H1N1	In vitro study	Quiroz et al., 2014
Quinic acid	Anti-dengue virus	In vitro study	Zanello et al., 2015
	Anti-hepatitis B virus	In vivo and in vitro study	Wang et al., 2009
	Anti-HIV-1-RT activity	Molecular docking study	Yazdi et al., 2019
Quercetin	Anti-dengue virus 2 (DENV2)	Molecular docking study	Ismail et al., 2017
	Anti-herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2)	In vitro study	Lyu et al., 2005
	Anti-influenza A virus	In vitro study	Wu et al.,2016
	Anti-hepatitis C virus	In vivo study	Rojas et al., 2016
	Anti-feline calicivirus (FCV) and murine norovirus (MNV)	In vivo study	Seo et al., 2016
	Anti-SARS coronavirus	In vivo study	Schwarz et al., 2014
Kaempferol	Anti-influenza B virus	In vitro study	Yang et al., 2014
	Anti-feline calicivirus (FCV)	In vivo study	Seo et al., 2016
	Anti-human cytomegalovirus	In vivo study	Mitrocotsa et al., 2000
	Anti-dengue virus and japanese encephalitis virus	In vivo study	Care et al., 2020
	Anti-japanese-encephalitis-virus	In vivo study	Zhang et al., 2012

	Anti-SARS coronavirus	In vivo study	Schwarz et al., 2014
	Anti-human rhinoviruses	In vitro study	Kwon et al., 2019
Epicatechin gallate	Anti-grass carp reovirus (GCRV)	In vitro study	Zhang et al., 2020
	Anti-feline calicivirus (FCV) and murine norovirus (MNV)	In vivo study	Seo et al., 2016
Quercetin-O-rhamnoside	Anti-influenza A virus	In vitro study	Choi et al., 2009
	Anti-influenza virus	In vitro and Molecular docking study	Gansukh et al., 2020

References:

- Care, C., Sornjai, W., Jaratsittisin, J., Hitakarun, A., Wikan, N., Triwitayakorn, K., & Smith, D. R. (2020). Discordant Activity of Kaempferol Towards Dengue Virus and Japanese Encephalitis Virus. Molecules, 25(5), 1246.
- Choi, H. J., Song, J. H., Park, K. S., & Kwon, D. H. (2009). Inhibitory effects of quercetin 3-rhamnoside on influenza A virus replication. European Journal of Pharmaceutical Sciences, 37(3-4), 329-333.
- Dai, X. Q., Cai, W. T., Wu, X., Chen, Y., & Han, F. M. (2017). Protocatechuic acid inhibits hepatitis B virus replication by activating ERK1/2 pathway and down-regulating HNF4α and HNF1α in vitro. Life Sciences, 180, 68-74.
- Ding, Y., Cao, Z., Cao, L., Ding, G., Wang, Z., & Xiao, W. (2017). Antiviral activity of chlorogenic acid against influenza A (H1N1/H3N2) virus and its inhibition of neuraminidase. Scientific reports, 7, 45723.
- Ferreira, P.G., Ferraz, A.C., Figueiredo, J.E., Lima, C.F., Rodrigues, V.G., Taranto, A.G., Ferreira, J.M.S., Brandão, G.C., Vieira-Filho, S.A., Duarte, L.P., de Brito Magalhães, C.L., de Magalhães, J.C., 2018. Detection of the antiviral activity of epicatechin isolated from Salacia crassifolia (Celastraceae) against Mayaro virus based on protein C homology modelling and virtual screening. Archives of Virology 163, 1567–1576. https://doi.org/10.1007/s00705-018-3774-1
- Gansukh, E., Nile, A., Kim, D. H., Oh, J. W., & Nile, S. H. (2020). New insights into antiviral and cytotoxic potential of quercetin and its derivatives-A biochemical perspective. Food Chemistry, 127508.
- Hassan, S. T., Švajdlenka, E., & Berchová-Bímová, K. (2017). Hibiscus sabdariffa L. and its bioactive constituents exhibit antiviral activity against HSV-2 and anti-enzymatic properties against urease by an ESI-MS based assay. Molecules, 22(5), 722.
- Ikeda, K., Tsujimoto, K., Uozaki, M., Nishide, M., Suzuki, Y., Koyama, A. H., & Yamasaki, H. (2011). Inhibition of multiplication of herpes simplex virus by caffeic acid. International Journal of Molecular Medicine, 28(4), 595-598.

- Ismail, N. A., & Jusoh, S. A. (2017). Molecular docking and molecular dynamics simulation studies to predict flavonoid binding on the surface of DENV2 E protein. Interdisciplinary Sciences: Computational Life Sciences, 9(4), 499-511.
- Kwon, M. J., Shin, H. M., Perumalsamy, H., Wang, X., & Ahn, Y. J. (2019). Antiviral effects and possible mechanisms of action of constituents from Brazilian propolis and related compounds. Journal of Apicultural Research, 1-13.
- Li, X., Liu, Y., Hou, X., Peng, H., Zhang, L., Jiang, Q., ... & Shi, W. (2013). Chlorogenic acid inhibits the replication and viability of enterovirus 71 in vitro. PLoS One, 8(9), e76007.
- Li, Y., But, P. P., & Ooi, V. E. (2005). Antiviral activity and mode of action of caffeoylquinic acids from Schefflera heptaphylla (L.) Frodin. Antiviral Research, 68(1), 1-9.
- Lu, F. J., Tseng, S. N., Li, M. L., & Shih, S. R. (2002). In vitro anti-influenza virus activity of synthetic humate analogues derived from protocatechuic acid. Archives of virology, 147(2), 273-284.
- Lyu, S. Y., Rhim, J. Y., & Park, W. B. (2005). Antiherpetic activities of flavonoids against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) in vitro. Archives of pharmacal research, 28(11), 1293-1301.
- Mitrocotsa, D., Mitaku, S., Axarlis, S., Harvala, C., & Malamas, M. (2000). Evaluation of the antiviral activity of kaempferol and its glycosides against human cytomegalovirus. Planta medica, 66(04), 377-379.
- Ogawa, M., Shirasago, Y., Ando, S., Shimojima, M., Saijo, M., & Fukasawa, M. (2018). Caffeic acid, a coffee-related organic acid, inhibits infection by severe fever with thrombocytopenia syndrome virus in vitro. Journal of infection and chemotherapy, 24(8), 597-601.
- Ou, C., Shi, N., Yang, Q., Zhang, Y., Wu, Z., Wang, B., ... & He, C. (2014). Protocatechuic acid, a novel active substance against avian Influenza virus H9N2 infection. PLoS One, 9(10), e111004.
- Quiroz, D. C. D., Carmona, S. B., Bolívar, F., & Escalante, A. (2014). Current perspectives on applications of shikimic and aminoshikimic acids in pharmaceutical chemistry. Research and Reports in Medicinal Chemistry, 4, 35-46.
- Ren, J., Huang, J., Yang, B., Lin, S., Li, J., Liao, H., Yuan, X., Wu, X., Ou, S., 2019. Docking and molecular dynamics: simulation of the inhibition of H5N1 influenza virus (Anhui 2005) neuraminidase (NA) by chlorogenic acid (CHA). International Journal of Clinical and Experimental Medicine 12, 9815–9823.
- Rojas, Á., Del Campo, J. A., Clement, S., Lemasson, M., García-Valdecasas, M., Gil-Gómez, A., ... & Negro, F. (2016). Effect of quercetin on hepatitis C virus life cycle: from viral to host targets. Scientific reports, 6(1), Seo, D. J., Jeon, S. B., Oh, H., Lee, B. H., Lee, S. Y., Oh, S. H., ... & Choi, C. (2016). Comparison of the antiviral activity of flavonoids against murine norovirus and feline calicivirus. Food control, 60, 25-30.
- Schwarz, S., Sauter, D., Wang, K., Zhang, R., Sun, B., Karioti, A., ... & Schwarz, W. (2014). Kaempferol derivatives as antiviral drugs against the 3a channel protein of coronavirus. Planta medica, 80(02-03), 177.
- Seo, D. J., Jeon, S. B., Oh, H., Lee, B. H., Lee, S. Y., Oh, S. H., ... & Choi, C. (2016). Comparison of the antiviral activity of flavonoids against murine norovirus and feline calicivirus. Food control, 60, 25-30.

- Serina, J.C., Castilho, P.C., Fernandes, M.X., 2017. Caffeoylquinic acids as inhibitors for HIV-I protease and HIV-I Integrase. A Molecular docking study. SDRP Journal of Computational Chemistry & Molecular Modelling 1. https://doi.org/10.25177/jccmm.1.2.1
- Sheng Xiehuang, Liu Wenqian, Xue Xia. Anti-herpes simplex virus effect of chlorogenic acid in vitro. chinese journal of natural medicines, 2008, 5, 6 (3) :232-234.
- Singh, P., Gupta, E., Mishra, N., & Mishra, P. (2020). Shikimic acid as intermediary model for the production of drugs effective against influenza virus. In Phytochemicals as Lead Compounds for New Drug Discovery (pp. 245-256). Elsevier.
- Song, J.M., Lee, K.H., Seong, B.L., 2005. Antiviral effect of catechins in green tea on influenza virus. Antiviral Research 68, 66–74. https://doi.org/10.1016/j.antiviral.2005.06.010
- Stankova, I., Chuchkov, K., Shishkov, S., Kostova, K., Mukova, L., & Galabov, A. S. (2009). Synthesis, antioxidative and antiviral activity of hydroxycinnamic acid amides of thiazole containing amino acid. Amino acids, 37(2), 383-388. 1-9.
- Urushisaki, T., Takemura, T., Tazawa, S., Fukuoka, M., Hosokawa-Muto, J., Araki, Y., & Kuwata, K. (2011). Caffeoylquinic acids are major constituents with potent anti-influenza effects in brazilian green propolis water extract. Evidence-Based Complementary and Alternative Medicine, 2011.
- Wang, G. F., Shi, L. P., Ren, Y. D., Liu, Q. F., Liu, H. F., Zhang, R. J., ... & Tao, P. Z. (2009). Anti-hepatitis B virus activity of chlorogenic acid, quinic acid and caffeic acid in vivo and in vitro. Antiviral research, 83(2), 186-190.
- Wu, W., Li, R., Li, X., He, J., Jiang, S., Liu, S., & Yang, J. (2016). Quercetin as an antiviral agent inhibits influenza A virus (IAV) entry. Viruses, 8(1), 6.
- Yang, Z. F., Bai, L. P., Huang, W. B., Li, X. Z., Zhao, S. S., Zhong, N. S., & Jiang, Z. H. (2014). Comparison of in vitro antiviral activity of tea polyphenols against influenza A and B viruses and structure–activity relationship analysis. Fitoterapia, 93, 47-53.
- Yazdi, S.E., Prinsloo, G., Heyman, H.M., Oosthuizen, C.B., Klimkait, T., Meyer, J.J.M., 2019. Anti-HIV-1 activity of quinic acid isolated from Helichrysum mimetes using NMR-based metabolomics and computational analysis. South African Journal of Botany 126, 328–339. https://doi.org/10.1016/j.sajb.2019.04.023
- Zanello, P. R., Koishi, A. C., Júnior, C. D. O. R., Oliveira, L. A., Pereira, A. A., de Almeida, M. V., ... & Bordignon, J. (2015). Quinic acid derivatives inhibit dengue virus replication in vitro. Virology journal, 12(1), 1-13.
- Zhang, T., Wu, Z., Du, J., Hu, Y., Liu, L., Yang, F., & Jin, Q. (2012). Anti-Japanese-encephalitis-viral effects of kaempferol and daidzin and their RNA-binding characteristics. PLoS One, 7(1), e30259.
- Zhang, Y., Wang, H., Su, M., & Lu, L. (2020). (-)-Epicatechin gallate, a metabolite of (-)-epigallocatechin gallate in grass carp, exhibits antiviral activity in vitro against grass carp reovirus. Aquaculture Research, 51(4), 1673-1680.