Electronic Supplementary Material (ESI) for RSC Advances.

Supplemental material

Nature as a treasure trove of potential anti-SARS-CoV drug leads: A structural/mechanistic rationale

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Table S1. List of previously reported anti-CoV natural products

Compound	Class	subclass	Target	Smile	IC50 (μM)	MW	Num. rotatable bonds	Num. H-bond acceptors	Num. H-bond donors	TPSA	Log P	Water Solubility	GI absorption	Lipinski	Veber	Bioavailability	Lead likeness	Synthetic accessibility
Tannic acid	Phenloics	Tannin	Mpro	C1=C(C=C(C(=C1O)O)O)C(=O)OC2=CC(=CC(=C2O)O)C(=O)OC[C@@H]3[C@H]([C@@H]([C@H]([C@@H](O3)OC(=O)C4=CC(=C(C(=C4)OC(=O)C5=CC(=C(C(=C5)O)O)O)O)O)OC(=O)C6=CC(=C(C(=C6)OC(=O)C7=CC(=C(C(=C7)O)O)O)O)O)OC(=O)C8=CC(=C(C(=C8)OC(=O)C9=CC(=C(C(=C9)O)O)O)O)O)OC(=O)C1=CC(=C(C(=C1)OC(=O)C1=CC(=C(C(=C1)O)O)O)O)O)O	3	1701.2	31	46	25	777.98	4.29	Yes	Low	No; 3 violations: MW>500, NorO>10, NHorOH>5	No; 2 violations: Rotors>10, TPSA>140	0.17	NO	10
Theaflavin 3,3-digallate	Phenloics	Tannin	Mpro	C1[C@H]([C@H](OC2=CC(=CC(=C21)O)O)C3=CC4=C(C(=C(C=C4[C@H]5[C@H](CC6=C(C=C(C=C6O5)	9.5	868.7	8	20	13	351.12	2.23	Yes	Low	No; 3 violations: MW>500, NorO>10,	No; 1 violation: TPSA>140	0.17	NO	6.36

				O)O)OC(=O)C7=CC(=C(C(=C7)O)O)O)O)O)C(=O)C(=C3)O)OC(=O)C8=CC(=C(C(=C8)O)O)O										NHorOH>5				
Dieckol	Phenloics	Tannin	Mpro	C1=C(C=C(C=C1O)OC2=C(C=C(C3=C2OC4=C(C=C(C=C4O3)OC5=C(C=C(C=C5O)OC6=C(C=C(C7=C6OC8=C(C=C(C=C8O7)O)O)O)O)O)O)O)O)O	15	742.55	6	18	11	287.14	2.66	Yes	Low	No; 3 violations: MW>500, NorO>10, NHorOH>6	No; 1 violation: TPSA>141	0.17	NO	4.68
Tetra-o-galloyl-beta-d-glucose	Phenloics	Tannin	ACE2-S	C1=C(C=C(C(=C1O)O)O)C(=O)OCC2C(C(C(C(O2)OC(=O)C3=CC(=C(C(=C3)O)O)O)O)OC(=O)C4=CC(=C(C(=C4)O)O)O)OC(=O)C5=CC(=C(C(=C5)O)O)O)O)O	4.2	788.57	13	22	13	377.42	0.07	Yes	Low	No; 3 violations: MW>500, NorO>10, NHorOH>7	No; 1 violation: TPSA>142	0.17	NO	5.92
Rhoifolin	Phenloics	Flavonoid	Mpro	C[C@H]1[C@@H]([C@H]([C@H]([C@@H](O1)O[C@@H]2[C@H]([C@@H]([C@H](O[C@H]2OC3=CC(=C4C(=C3)OC(=CC4=O)C5=CC=C(C=C5)O)O	27.45	578.52	6	14	8	228.97	1.31	Yes	Low	No; 3 violations: MW>500, NorO>10, NHorOH>7	No; 1 violation: TPSA>142	0.17	NO	6.33

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Epigallocatechin gallate	Phenloics	Flavonoid	Mpro	C1[C@H]([C@H](OC2=CC(=CC(=C21)O)O)C3=CC(=C(C(=C3)O)O)O)OC(=O)C4=CC(=C(C(=C4)O)O)O	73	458.37	4	11	8	197.37	1.53	Yes	Low	No; 3 violations: MW>500, NorO>10, NHorOH>8	No; 1 violation: TPSA>143	0.17	NO	4.2
Gallocatechin gallate	Phenloics	Flavonoid	Mpro	C1[C@H]([C@@H](OC2=CC(=CC(=C21)O)O)C3=CC(=C(C(=C3)O)O)O)OC(=O)C4=CC(=C(C(=C4)O)O)O	47	458.37	4	11	8	197.37	1.83	Yes	Low	No; 3 violations: MW>500, NorO>10, NHorOH>9	No; 1 violation: TPSA>144	0.17	NO	4.2
Pectolinarin	Phenloics	Flavonoid	Mpro	C[C@H]1[C@@H]([C@H]([C@H]([C@@H](O1)OC[C@@H]2[C@H]([C@@H]([C@H]([C@@H](O2)OC3=C(C(=C4C(=C3)OC(=CC4=O)C5=CC=C(C=C5)OC)O)OC)O)O)O)O)O)O	73.78	622.57	8	15	7	227.2	3.41	Yes	Low	No; 3 violations: MW>500, NorO>10, NHorOH>8	No; 1 violation: TPSA>143	0.17	NO	6.63
Herbacetin	Phenloics	Flavonoid	Mpro	C1=CC(=CC=C1C2=C(C(=O)C3=C(O2)C(=CC=C3O)O)O)O)	33.17	302.24	1	7	5	131.36	1.5	Yes	High	Yes	Yes	0.55	Yes	3.2

				O														
Hesperetin	Phenloics	Flavonoid	Mpro	COC1=C(C=C(C=C1)[C@@H]2CC(=O)C3=C(C=C(C=C3O2)O)O)O	18.1	302.28	2	6	3	96.22	2.24	Yes	High	Yes	Yes	0.55	Yes	3.02
Daidzein	Phenloics	Flavonoid	Mpro	C1=CC(=CC=C1C2=COC3=C(C2=O)C=CC(=C3)O)O	26.8	254.24	1	4	2	70.67	1.77	Yes	High	Yes	Yes	0.55	Yes	2.79
Hyperoside	Phenloics	Flavonoid	Mpro	c1cc(c(cc1c2c(c(=O)c3c(cc(cc3o2)O)O)O[C@H]4[C@@H]([C@H]([C@H]([C@H](O4)CO)O)O)O)O)O	42.79	464.38	4	12	8	210.51	1.45	Yes	Low	No; 2 violations: NorO>10, NHorOH>5	No; 1 violation: TPSA>140	0.17	NO	5.32
Apigenin	Phenloics	Flavonoid	Mpro	O=C1C=C(C2=CC=C(O)C=C2)OC3=CC(O)=CC(O)=C31	200	270.24	1	5	3	90.9	1.89	Yes	High	Yes	Yes	0.55	Yes	2.96
Luteolin	Phenloics	Flavonoid	Mpro	O=C1C=C(C2=CC=C(O)C(O)=C2)OC3=CC(O)=CC(O)=C31	20	286.24	1	6	4	111.13	1.86	Yes	High	Yes	Yes	0.55	Yes	3.02
Quercetin	Phenloics	Flavonoid	Mpro	O=C1C(O)=C(C2=CC=C(O)C(O)=C2)OC3=CC(O)=CC(O)=C31	83.1	302.24	1	7	5	131.36	1.63	Yes	High	Yes	Yes	0.55	Yes	3.23
Scutellarein	Phenloics	Flavonoid	Mpro	C1=CC(=CC=C1C2=CC(=O)C3=C(O2)C=C(C(=C3O)O)O)O	33.1	286.24	1	6	4	111.13	2.08	Yes	High	Yes	Yes	0.55	Yes	3.04

Quercetagetin	Phenloics	Flavonoid	Mpro	C1=CC(=C(C=C1C2=C(C(=O)C3=C(O2)C=C(C(=C3O)O)O)O)O)O	12	318.24	1	8	6	151.59	1.73	Yes	Low	Yes	No; 1 violation: TPSA>140	0.55	Yes	3.27
Myricetin	Phenloics	Flavonoid	Mpro	C1=C(C=C(C(=C1O)O)O)C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O	34.6	318.24	1	8	6	151.59	1.73	Yes	Low	Yes	No; 1 violation: TPSA>141	0.55	Yes	3.27
Robinetin	Phenloics	Flavonoid	Mpro	C1=CC2=C(C=C1O)OC(=C(C2=O)O)C3=CC(=C(C(=C3)O)O)O	67.2	302.24	1	7	5	131.36	1	Yes	High	Yes	Yes	0.55	Yes	3.21
Amentoflavone	Phenloics	Flavonoid	Mpro	O=C1C=C(C2=CC=C(O)C=C2)OC3=C(C4=C(O)C=CC(C5=CC(C(C(O)=CC(O)=C6)=C6O5)=O)=C4)C(O)=CC(O)=C31	8.3	538.46	3	10	6	181.8	3.06	NO	Low	No; 2 violations: MW>500, NHorOH>5	No; 1 violation: TPSA>140	0.17	NO	4.27
Flavonoid Derivative	Phenloics	Flavonoid	PLpro	OC(C(OC)=C1)=CC=C1[C@@H]2[C@@H](O)C(C3=C(O)C4=C(O[C@](CCCC(C)(O)C)(C)CC4)C=C3C2)=O	5	470.55	6	7	4	116.45	3.24	Moderate	High	Yes	Yes	0.55	Yes	5.01
Papyriflavonol A	Phenloics	Flavonoid	PLpro	CC(=CCC1=C(C(=CC(=C1)C2=C(C(=O)C3=C(O2)C=C(C(=C3O)CC=C(C)C)	3.7	438.47	5	7	5	131.36	3.69	Moderate	Low	Yes	Yes	0.55	Yes	4.24

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Kaempferol	Phenloics	Flavonoid	PLpro	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O	16.3	286.24	1	6	4	111.13	1.7	Yes	High	Yes	Yes	0.55	Yes	3.14
Bavachinin	Phenloics	Flavonoid	PLpro	CC(=CCC1=CC2=C(C=C1OC)O[C@@H](CC2=O)C3=CC=C(C=C3)O)C	38.4	338.4	4	4	1	55.76	3.47	Moderate	High	Yes	Yes	0.55	Yes	3.7
Neobavaisoflavone	Phenloics	Flavonoid	PLpro	CC(=CCC1=C(C=CC(=C1)C2=COC3=C(C2=O)C=CC(=C3)O)O)C	18.3	322.35	3	4	2	70.67	3.03	Moderate	High	Yes	Yes	0.55	Yes	3.35
Corylifol A	Phenloics	Flavonoid	PLpro	CC(=CCC/C(=C/CC1=C(C=CC(=C1)C2=COC3=C(C2=O)C=CC(=C3)O)O)/C)C	32.3	390.47	6	4	2	70.67	3.83	NO	High	Yes	Yes	0.55	Yes	3.86
Juglanin	Phenloics	Flavonoid	Cath	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O[C@H]4[C@@H]([C@H]([C@@H](O4)CO)O)O)O	2.5	418.35	4	10	6	170.05	1.76	Yes	Low	Yes	No; 1 violation: TPSA>140	0.55	Yes	5
Baicalin	Phenloics	Flavonoid	Misc	C1=CC=C(C=C1)C2=CC(=O)C3=C(C(=C(C=C3O2)O[C@H]4[C@@H]([C@H]([C@@H]([C@H](O4)C(=O)	25	446.36	4	11	6	187.12	1.75	Yes	Low	No; 3 violations: MW>500, NorO>10,	No; 1 violation: TPSA>140	0.17	NO	5.09

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Procyanidin A2	Phenloics	Flavonoid	Misc	C1[C@H]([C@H](OC2=C1C(=CC3=C2[C@@H]4[C@H]([C@](O3)(OC5=CC(=CC(=C45)O)O)C6=CC(=C(C=C6)O)O)O)C7=CC(=C(C=C7)O)O)O	3.4	576.5	2	12	9	209.76	1.73	Moderate	Low	No; 3 violations: MW>500, NorO>10, NHorOH >5	No; 1 violation: TPSA>140	0.17	NO	5.85
Procyanidin B1	Phenloics	Flavonoid	Misc	C1[C@@H]([C@H](OC2=C1C(=CC(=C2[C@@H]3[C@H]([C@H](OC4=CC(=CC(=C34)O)O)C5=CC(=C(C=C5)O)O)O)O)O)C6=CC(=C(C=C6)O)O)O	41.3	578.52	3	12	10	220.76	1.27	Yes	Low	No; 3 violations: MW>500, NorO>10, NHorOH >5	No; 1 violation: TPSA>140	0.17	NO	5.32
Myricetin	Phenloics	Flavonoid	Hilcase	C1=C(C=C(C(=C1O)O)O)C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O	44.3	318.24	1	8	6	151.59	1.08	Yes	Low	Yes	No; 1 violation: TPSA>140	0.55	NO	3.27
Scutellarein	Phenloics	Flavonoid	Hilcase	C1=CC(=CC=C1C2=CC(=O)C3=C(O2)C=C(C(=C3O)O)O)O	34.6	286.24	1	6	4	111.13	2.08	Yea	High	Yes	Yes	0.55	Yes	3.04
Isoliquiritigenin	Phenloics	Chalcones	PLpro	C1=CC(=CC=C1/C=C/C(=O)C2=C(C=C(C=C2)O)O)O	24.6	256.25	3	4	3	77.76	2.02	Yes	High	Yes	Yes	0.55	Yes	2.52

Isobavachalcone	Phenloics	Chalcones	PLpro	CC(=CCC1=C(C=CC(=C1O)C(=O)/C=C/C2=CC=C(C=C2)O)O)C	7.3	324.37	5	4	3	77.76	3.02	Moderate	High	Yes	Yes	0.55	Yes	3.03
4'-O-methylbavachalcone	Phenloics	Chalcones	PLpro	CC(=CCC1=CC(=C(C=C1OC)O)C(=O)/C=C/C2=CC=C(C=C2)OC)C	10.1	352.42	7	4	1	55.76	4.07	Moderate	High	Yes	Yes	0.55	Yes	3.21
Chalcone 1	Phenloics	Chalcones	Mpro	OC(C=C1)=CC=C1/C=C/C(C2=C(O)C(C/C=C(C)/C)=C(O)C=C2)=O	11.9	324.37	5	4	3	77.76	3.02	Moderate	Low	Yes	Yes	0.55	Yes	3.03
Chalcone 2	Phenloics	Chalcones	Mpro	OC(C=C1)=CC=C1/C=C/C(C2=C(O)C(C/C=C(C)/CC/C=C(C)/C)=C(O)C=C2)=O	5.8	392.49	8	4	3	77.76	4.06	NO	High	Yes	Yes	0.55	Yes	3.57
Chalcone 3	Phenloics	Chalcones	Mpro	OC(C=C1)=CC=C1/C=C/C(C2=C(O)C(C[C@H](O)C(C)=C)=C(OC)C=C2)=O	9.3	354.4	7	5	3	86.99	2.87	Moderate	High	Yes	Yes	0.55	Yes	3.64
Chalcone 4	Phenloics	Chalcones	Mpro	OC(C=C1)=CC=C1/C=C/C(C2=C(O)C(C/C=C(C)/CC[C@H](O)C(C)=C)=C(O)C=C2)=O	8.6	354.4	7	5	3	86.99	2.87	Moderate	High	Yes	Yes	0.55	Yes	4.03
Chalcone 5	Phenloics	Chalcones	Mpro	OC(C=C1)=C(O)C=C1/C=C/C(C2=C(O)C(C/C	27.9	340.37	5	5	4	97.99	2.54	Moderate	High	Yes	Yes	0.55	Yes	3.13

				=C(C)/C)=C(O)C=C2)=O														
Chalcone 6	Phenloics	Chalcones	Mpro	OC(C(O)=C1)=C(C/C=C(C)/C)C=C1C2OC3=CC(O)=CC=C3CC2	34.7	326.39	3	4	3	69.92	2.97	Moderate	High	Yes	Yes	0.55	Yes	3.71
N-trans-caffeoyltyramine	Phenloics	Cinnamic acids	PLpro	C1=CC(=CC=C1CCNC(=O)/C=C/C2=CC(=C(C=C2)O)O)O	44.4	299.32	6	4	4	89.79	2.00 2.00	Yes	High	Yes	Yes	0.55	Yes	2.43
N-trans-coumaroyltyramine	Phenloics	Cinnamic acids	PLpro	C1=CC(=CC=C1CCNC(=O)/C=C/C2=CC=C(C=C2)O)O	38.8	283.32	6	3	3	69.56	2.05	Yes	High	Yes	Yes	0.55	Yes	2.28
N-trans-feruloyltyramine	Phenloics	Cinnamic acids	PLpro	COC1=C(C=CC(=C1)/C=C/C(=O)NCCC2=CC=C(C=C2)O)O	70.1	313.35	7	4	3	78.79	2.58	Yes	High	Yes	Yes	0.55	Yes	2.55
Terrestriamide	Phenloics	Cinnamic acids	PLpro	COC1=C(C=CC(=C1)/C=C/C(=O)NCC(=O)C2=CC=C(C=C2)O)O	21.5	327.33	7	5	3	95.86	2.02	Yes	High	Yes	Yes	0.55	Yes	2.55
N-trans-feruloyloctopamine	Phenloics	Cinnamic acids	PLpro	COC1=C(C=CC(=C1)/C=C/C(=O)NCC(C2=CC=C(C=C2)O)O)O	23.2	329.35	7	5	4	99.02	2.22	Yes	High	Yes	Yes	0.55	Yes	3.05
Psoralidin	Phenloics	Cinnamic acids	PLpro	CC(=CCC1=CC2=C(C=C1O)OC(=O)C3=C2OC4=C3C=CC(=C4)O)C	4.2	336.34	2	5	2	83.81	3.15	NO	High	Yes	Yes	0.55	Yes	3.4

Emodin	Phenloics	Anthraquinone	ACE2-S	O=C2c1cc(cc(O)c1C(=O)c3c2cc(O)cc3O)C	1	270.24	0	5	3	94.83	1.81	Yes	High	Yes	Yes	0.55	Yes	2.57
Rhein	Phenloics	Anthraquinone	ACE2-S	C1=CC2=C(C(=C1)O)C(=O)C3=C(C=C(C=C3C2=O)C(=O)O)O	9.5	284.22	1	6	3	111.9	1.37	Yes	High	Yes	Yes	0.55	Yes	2.58
Aloeemodin	Phenloics	Anthraquinone	Mpro	C1=CC2=C(C(=C1)O)C(=O)C3=C(C2=O)C=C(C=C3O)CO	35.7	270.24	1	5	3	94.83	1.95	Yes	High	Yes	Yes	0.55	Yes	2.6
Heptanoid Drevative	Phenloics	Heptanoid	Plpro	O=C(/C=C/CCC1=CC=C(O)C(O)=C1)CCC2=CC(O)=C(O)C=C2	4.1	328.36	7	5	4	97.99	2.02	Yes	High	Yes	Yes	0.55	Yes	2.48
Indigo	Alkaloid	Isatin	Mpro	C1=CC=C2C(=C1)C(=C(N2)C3=NC4=CC=CC=C4C3=O)O	37.3	262.26	1	3	2	65.45	2.19	Yes	High	Yes	Yes	0.55	Yes	2.95
Indirubin	Alkaloid	Isatin	Mpro	C1=CC=C2C(=C1)C(=C(N2)O)C3=NC4=CC=CC=C4C3=O	81.3	262.26	1	3	2	65.45	2.13	Yes	High	Yes	Yes	0.55	Yes	2.84
Indican	Alkaloid	Isatin	Mpro	C1=CC=C2C(=C1)C(=CN2)O[C@H]3[C@@H]([C@H]([C@@H]([C@H](O3)CO)O)O)O	33.1	295.29	3	6	5	115.17	0.64	Yes	High	Yes	Yes	0.55	Yes	4.23
Tryptanthrin	Alkaloid	Isatin	PLpro	C1=CC=C2C(=C1)C(=O)N3C4=CC=CC=C4C(=O)C3=N2	1.52	248.24	0	3	0	51.96	1.95	Yes	High	Yes	Yes	0.55	Yes	2.42

Indigodole B	Alkaloid	Isatin	PLpro	O=C2c1c(cccc1)N3C(=O)c4c(N[C@]23CC)cccc4	2.6	278.31	1	2	1	49.41	2.3	Yes	High	Yes	Yes	0.55	Yes	3
Sinigrin	Alkaloid	thioglycoside	Mpro	C=CC/C(=N\OS(=O)(=O)O)/S[C@H]1[C@@H]([C@H]([C@@H]([C@H](O1)CO)O)O)O	50.3	359.37	7	10	5	199.79	0.96	Yes	Low	Yes	No; 1 violation: TPSA>140	0.11	NO	5.35
Lycorine	Alkaloid	Indole	Misc	C1CN2CC3=CC4=C(C=C3[C@H]5[C@H]2C1=C[C@@H]([C@H]5O)O)OCO4	15.7	287.31	0	5	2	62.16	2.42	Yes	High	Yes	Yes	0.17	Yes	4.2
Reserpine	Alkaloid	Indole	Misc	CO[C@H]1[C@@H](C[C@@H]2CN3CCC4=C([C@H]3C[C@@H]2[C@@H]1C(=O)OC)NC5=C4C=CC(=C5)OC)OC(=O)C6=CC(=C(C(=C6)OC)OC)OC	3.4	608.68	10	10	1	117.78	5.16	NO	High	No; 2 violations: NorO>10, NHorOH>5	No; 2 violations: NorO>10, NHorOH>5	0.56	NO	5.92
MDL28170	Peptide	Small peptide	Cath	CC(C)[C@@H](C(=O)N[C@@H](CC1=CC=CC=C1)C=O)NC(=O)OCC2=CC=CC=C2	0.0025	382.45	12	4	2	84.5	2.62	NO	Low	Yes	No; 1 violation: TPSA>141	0.55	NO	3.67
Tokaramide A	Peptide	Small peptide	Mpro	O=C(N[C@@H](C(C)C)C(N[C@@H](C(C)C)C(N[C@H](C([	5.6	476.57	17	6	7	186.5	1.58	Yes	Low	No; 2 violations: NorO>1	No; 2 violations: Rotors>	0.17	NO	4.09

				H])=O)CCCNC(N)=N)=O)=O)C1=CC=C(O)C=C1										0, NHorOH >5	10, TPSA>140			
Miraziridine A	Peptide	Small peptide	Mpro	OC(C(N1)C1C(N[C@H](CC(C)C)C(N[C@@H](CC(C)C)[C@@H](O)CC(N[C@H](CC)C(N[C@@H](CCCNC(N)=N)/C=C/C(O)=O)=O)=O)=O)=O)=O	6.8	668.78	27	11	11	295.07	0.8	Yes	Low	No; 2 violations: NorO>10, NHorOH >6	No; 2 violations: Rotors>10, TPSA>141	0.17	NO	6.65
Betulinic acid	Terpenes	Triterpene	Mpro	CC(=C)[C@@H]1CC[C@]2([C@H]1[C@H]3CC[C@@H]4[C@]5(CC[C@@H](C([C@@H]5CC[C@]4([C@@]3(CC2)C)C)(C)C)O)C)C(=O)O	8.2	456.7	2	3	2	57.53	3.81	NO	Low	Yes	Yes	0.56	Yes	5.63
Saikosaponin B2	Terpenes	Triterpene	Misc	C[C@@H]1[C@@H]([C@@H]([C@H]([C@@H](O1)O[C@H]2CC[C@]3([C@H]([C@]2(CO)CC[C@@]4([C@@H]3C=CC5=C6CC(CC[C@@]6([C@@H](C[C@]54C)O)CO)(C)C)C)O)O[C@H]7[C@@H]([C@	1.7	780.98	7	13	9	218.99	3.47	Yes	Low	No; 3 violations: MW>500, NorO>10, NHorOH >5	No; 1 violation: TPSA>140	0.17	NO	9.17

				H]([C@@H]([C@H](O7)CO)O)O)O)O														
Aescin	Terpenes	Triterpene	Misc	C/C=C(/C)\C(=O)O[C@H]1[C@@H]([C@@]2([C@@H](C[C@@]3(C(=CC[C@H]4[C@]3(CC[C@@H]5[C@@]4(CC[C@@H]([C@]5(C)CO)O[C@H]6[C@@H]([C@H]([C@@H]([C@H](O6)C(=O)O)O[C@H]7[C@@H]([C@H]([C@@H]([C@H](O7)CO)O)O)O)O)O[C@H]8[C@@H]([C@H]([C@@H]([C@H](O8)CO)O)O)O)C)C)[C@@H]2CC1(C)CC)O)CO)OC(=O)C	6	1131.26	16	24	13	388.04	3.43	Yes	Low	No; 3 violations: MW>500, NorO>10, NHorOH>5	No; 1 violation: TPSA>140	0.11	NO	10
Savinin	Terpenes	Phenolic terpene	Mpro	C1[C@@H](/C(=C\C2=CC3=C(C=C2)OCO3)/C(=O)O1)CC4=CC5=C(C=C4)OCO5	9.1	352.34	3	6	0	63.22	2.86	Moderate	High	Yes	Yes	0.55	Yes	3.62
Pseurata A	Terpenes	Sesterterpene	Mpro	C[C@@]12CC[C@H](C([C@H]1C[C@H]([C@]34C2CC[C@H	56.6	334.45	0	4	3	77.76	2.32	Yes	High	Yes	Yes	0.55	Yes	5.91

				]([C@H]3O)C(=C)C4=O)O)(C)C)O														
Pseurata B	Terpenes	Sesterterpene	Mpro	C[C@@]12CC[C@H](C([C@H]1C[C@H]([C@]34C2CC[C@H]([C@H]3O)C(=C)C4=O)O)(C)C)O	32.2	334.45	0	4	3	77.76	2.32	Yes	High	Yes	Yes	0.55	Yes	5.91
Pseurata C	Terpenes	Sesterterpene	Mpro	CC(=O)O[C@H]1CC[C@@]2([C@@H](C1(C)C)C[C@H]([C@]34[C@H]2CC(=O)[C@H]([C@H]3O)C(=C)C4=O)O)C	29.2	390.47	2	6	2	100.9	-2.21	Yes	High	Yes	Yes	0.55	Yes	6.02
Leukamenin E	Terpenes	Sesterterpene	Mpro	CC(=O)O[C@H]1CC[C@@]2([C@@H](C1(C)C)C[C@H]([C@]34[C@H]2CC(=O)[C@H]([C@H]3O)C(=C)C4=O)O)C	45.5	376.49	2	5	2	83.83	-1.52	Yes	High	Yes	Yes	0.55	Yes	6.02
Glaucocalyxin B	Terpenes	Sesterterpene	Mpro	CC(=O)O[C@@H]1[C@H]2CC[C@@H]3[C@]1([C@@H]([C[C@H]4[C@]3(CCC(=O)C4(C)C)C)O)C(=O)C2=C	58.6	374.47	2	5	1	80.67	2.09	Yes	High	Yes	Yes	0.55	Yes	5.99
Liangshani	Terpenes	Sesterter	Mpro	C[C@@]12C=CC(=O)C([C@H]	23.2	330.4	0	4	2	74.6	1.99	Yes	High	Yes	Yes	0.55	Yes	5.95

n A.		pene		1C[C@H]([C@]34[C@H]2CC[C@H]([C@H]3O)C(=C)C4=O)O)(C)C		2												
Tanshinone 1	Terpenes	Sesterterpene	Plpro	O=C(C1=C(C2=C3C(C)CO2)C=CC4=C1CCCC4(C)C)C3=O	0.8	296.36	0	3	3	43.37	2.81	Moderate	High	Yes	Yes	0.56	Yes	4.11
Beta-sitosterol	Sterol	Sterol	Mpro	CC[C@H](CC[C@@H](C)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C)C)C(C)C	47.8	414.71	6	1	1	20.23	5.05	NO	Low	Yes	Yes	0.55	Yes	6.3

Table S2. Top Hits retrieved from *in silico* virtual screening against COVID 19 M^{pro}.

No.	Hit	Compound	Binding Energy (kcal/mol)	RMSD (Å)	Binding interactions
1	3,4 Dihydroxyphenylglycol	$C_8H_{10}O_4$	-11.5476351	1.60000	Gln 189, Thr 190,

					Gln 192
2	Coniferyl aldehyde	$C_{10}H_{10}O_3$	-10.5984106	1.200000	Gln 189, Thr 190, Met 165
3	Ellagic acid	$C_{14}H_6O_8$	-14.4139233	0.000000000	Gln 189, Thr 190, Met 165, Glu 166
4	Gluco-p-coumaric acid	$C_{15}H_{18}O_8$	-11.9070959	3.5999999	Gln 189, Thr 190, Met 165, Gln 192, Arg 188
5	Isoxanthohumol	$C_{21}H_{22}O_5$	-12.6585665	1.20000005	Gln 189, Thr 190, Glu 166, Cys 145
6	Ellagic acid glucoside	$C_{20}H_{16}O_{13}$	-14.7417517	1.79999995	ASN 142, MET 165, CYS 145, THR 26, GLY 143, GLN 189
7	Acetylglucopetunidin	$C_{24}H_{25}O_{13}^+$	-15.2547722	0.000000000	Gln 189, Asn 182, Glu 166, Cys 145
8	Spiraeoside	$C_{21}H_{20}O_{12}$	-16.2750187	0.747515559	Gln 192, Glu 166, His 41, Cys 44, Met 49
9	Kaempferol 3-O-(6-malonyl-glucoside)	$C_{24}H_{22}O_{14}$	-13.8481274	0.600000024	Gln 189, Thr 190, Glu 166
10	Narirutin	$C_{27}H_{32}O_{14}$	-12.9922199	1.20129132	Thr 190, His 41, Ser 49
11	Tulipanin	$C_{27}H_{31}O_{16}^+$	-13.7354822	1.80000293	Gln 189, His 41, Met 165
12	Spinacetin 3-[feruloyl-(->2)-glucosyl-(1->6)-[apiosyl-(1->2)]-glucoside]	$C_{44}H_{50}O_{25}$	-12.7176895	0.800000012	Gln 192, Glu 166, His 41, Cys 44, Met 49

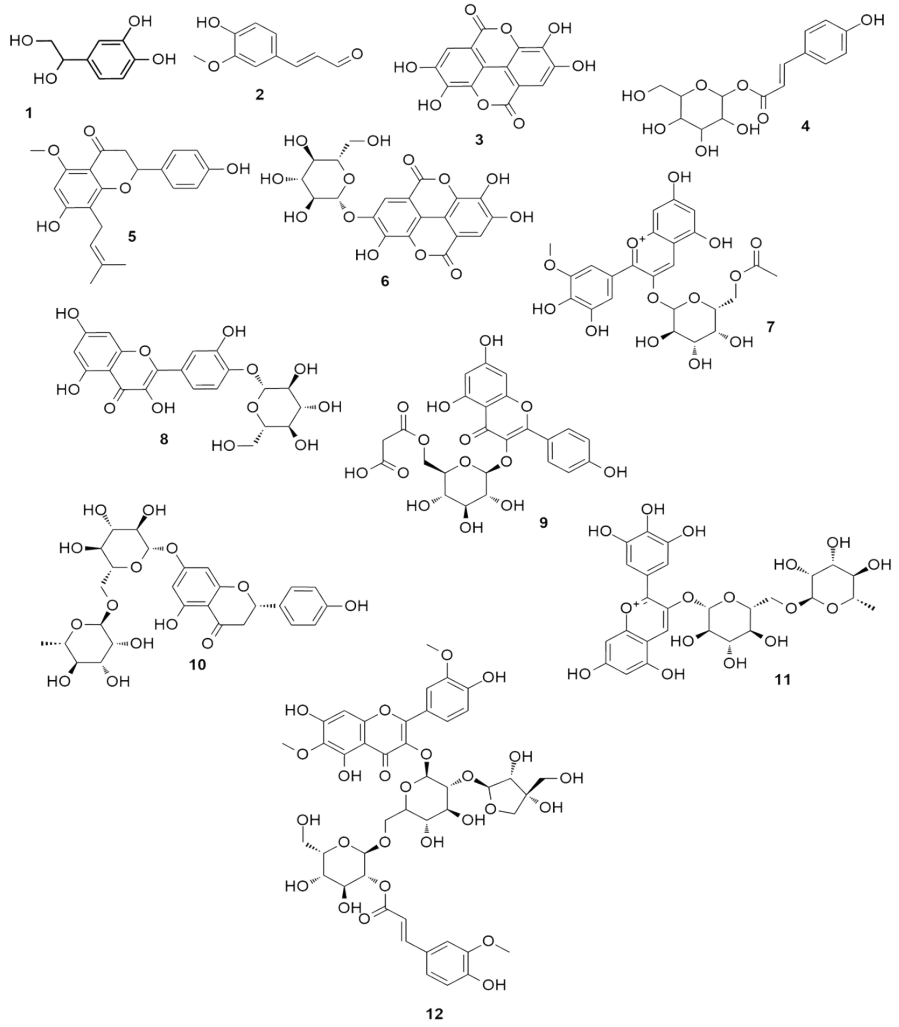

Figure S1. Structures of the top Hits retrieved from in silico virtual screening against SARS-CoV M^{pro}.

Methodology

Drug-likeness analysis

Drug-like properties of the reported anti-SARS-CoV natural products (Table S1) were predicted by the commercially available software LigandScout 4.3. A list of smile codes of these compounds was prepared and submitted to the software to perform the drug-likeness calculations (e.g. molecular weight, hydrogen bonds donor, hydrogen bonds acceptor, number of rotatable bonds, topological polar surface area, and logP). Subsequently, the results were exported to Microsoft Excel for the statistical analysis and figures preparation.

Virtual Screening and Molecular Docking.

All molecular docking and virtual screening studies were carried out using 'Molecular Operating Environment 2019.0101' software (MOE of Chemical Computing Group Inc. on Core i5 2.2 GHz workstation running on a Windows 10 PC. A phenolics library was selected depending on previously reported compounds for the docking-based virtual screening study. This library contains 496 compounds that can be free downloaded in 3D format in a ready-to-dock stage from (http://phenol-explorer.eu/). Docking of ligands onto the binding site of the COVID-19 protease enzyme was performed using the automated docking software that applies initial rescoring methodology (London dG) after docking through placement, using Triangle Matcher protocol to define the best poses of the ligand based on its binding interaction pattern with the protein. The 3D structure of the COVID-19 main protease in complex with its ligand (PDB code: 5R7Z) was available from protein data bank (PDB) at (RCSB). Three dimensional structures of the ligands, their protonation, and minimization were performed using the systemic search, for each ligand 10 different poses were analyzed and 500 top-scored ligands were investigated carefully using molecular visualization. The poses were chosen regarding their hydrophobic, and hydrogen bond interactions. On the other hand, the poses that have shown alternative binding modes in the binding site were also given special attention.