Supporting Information for

Original article

Schaftoside inhibits 3CL^{pro} and PL^{pro} of SARS-CoV-2 virus and regulates immune response and inflammation of host cells for the treatment of COVID-19

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1. Supporting methods

1.1. Experimental details for proteomics analysis

Vero E6 cells were infected with SARS-CoV-2 virus, or with schaftoside and SARS-CoV-2 for 24 h (MOI=1), respectively. The sample was sonicated three times on ice using a high intensity ultrasonic processor (Scientz) in lysis buffer (8 mmol/L urea, 1% protease inhibitor cocktail). The debris was removed by centrifugation at 12,000 × *g* at 4 °C for 10 min. The supernatant was then collected and the protein concentration was measured by BCA kit. The sample was added with one volume of pre-cooled acetone, vortexed to mix, and then added with four

volumes of pre-cooled acetone, precipitated at –20 °C for 2 h. The sample was then redissolved in 200 mmol/L TEAB and ultrasonically dispersed. For the first digestion overnight, trypsin was added at 1:50 trypsin-to-protein mass ratio. The sample was reduced with 5 mmol/L dithiothreitol for 60 min at 37 °C and alkylated with 11 mmol/L iodoacetamide for 45 min at room temperature in darkness. The peptides were desalted on a Strata X SPE column. Tryptic peptides were dissolved in 0.5 mmol/L TEAB. Each channel of peptide was labeled by their respective TMT reagent (based on manufacturer's protocol, ThermoFisher Scientific), and incubated for 2 h at room temperature. An aliquot of 5 μL of each sample was pooled, desalted and analyzed by MS to check labeling efficiency. Then, samples were quenched by adding 5% hydroxylamine. The pooled samples were desalted with a Strata X C18 SPE column (Phenomenex) and dried by vacuum centrifugation.

The tryptic peptides were dissolved in solvent A (0.1% formic acid and 2% acetonitrile in water), directly loaded onto a home-made reversed-phase analytical column (25 cm length, 75 μm i.d.). Peptides were separated with a gradient from 5% to 25% solvent B (0.1% formic acid in 90% acetonitrile) over 60 min, 25% to 35% in 22 min, and up to 80% in 4 min, and then held at 80% for 4 min, all at a constant flow rate of 450 nL/min on an EASY-nLC 1200 UPLC system (ThermoFisher Scientific). The separated peptides were characterized by a Q Exactive HF-X mass spectrometer (ThermoFisher Scientific) with a nano-electrospray ion source. The electrospray voltage was 2.0 kV and the full MS scan resolution was set to 60,000 for a scan range of *m*/*z* 350–1600. Up to 20 most abundant precursor ions were selected for MS/MS analyses with 30-s dynamic exclusion. The HCD fragmentation was performed at a normalized collision energy (NCE) of 28% and the fragments were detected in the Orbitrap at a resolution of 30,000. Fixed first mass was set at *m*/*z* 100. Automatic gain control (AGC) target was set at 1E5, with an intensity threshold of 3.3E4 and a maximum injection time of 60 ms.

1.2. Pharmacokinetic study

Male C57BL/6J mice (20 g) were provided by the Experimental Animal Center of Peking University Health Science Center (Beijing, China). Schaftoside (150 mg/kg) was given by

intraperitoneal injection. Blood samples were collected from rat orbit into heparinized tubes at 1, 4, 8, 10, 12, 24, and 48 h, respectively, and were immediately centrifuged at 15,000 rpm (Eppendorf, Centrifuge 5424R, Germany, 4 °C) for 30 min to obtain the plasma. Then 100 μL of plasma sample was mixed with 300 μL of methanol and 100 μL IS solution (internal standard, 5 μg/mL orientin in methanol). The mixture was vortexed to precipitate protein and then centrifuged at 15,000 rpm for 30 min. The supernatant was separated, dried, and then dissolved in 100 μL of 50% methanol. The sample was centrifuged (15,000 rpm for 30 min) and the supernatant was analyzed by LC–MS/MS. Samples were separated on a Waters Acquity UPLC BEH C18 column (1.7 μmol/L, 2.1 mm×50 mm) (Waters, USA). The column temperature was 30 °C. The mobile phase consisted of water containing 0.1% formic acid (*v*/*v*, A) and acetonitrile (B). A 5-min gradient elution program was used: 0–1 min, 10%–50% B; 1–2 min, 50%–90% B; 2–3 min, 90% B; 3.1–5 min, 10% B. The flow rate was 0.3 mL/min. The injection volume was 2 μL. Mass spectrometry analysis was performed on an API 4000 QTRAP mass spectrometer equipped with a TurboIonSpray source (Foster City, USA). Schaftoside and orientin (IS) were determined by multiple reaction monitoring (MRM) in the negative ion mode, with MRM transitions of *m*/*z* 563.5→353.0 and *m*/*z* 447.4→327.0, respectively. The data were analyzed by Analyst 1.4.1 software. For schaftoside, the regression equation was y=0.000331x–0.00063 (r=0.9998), where y represents the ratio of schaftoside peak area to IS peak area, x the concentration (ng/mL), and r the correlation coefficient. The linear range was from 5–5000 ng/mL.

2. Supporting figures

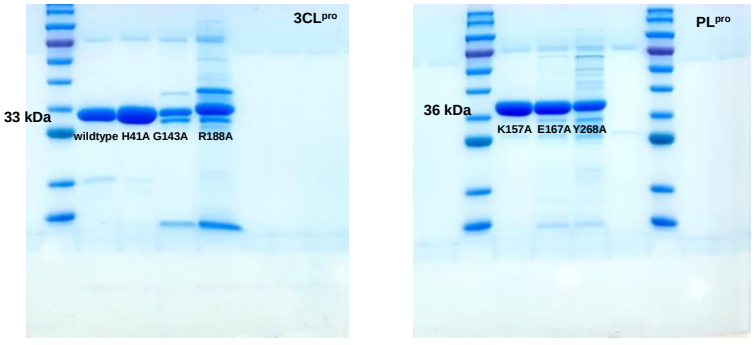

Figure S1 SDS-PAGE of non-tagged SARS-CoV-2 virus $3CL^{pro}$, PL^{pro}, and their mutants.

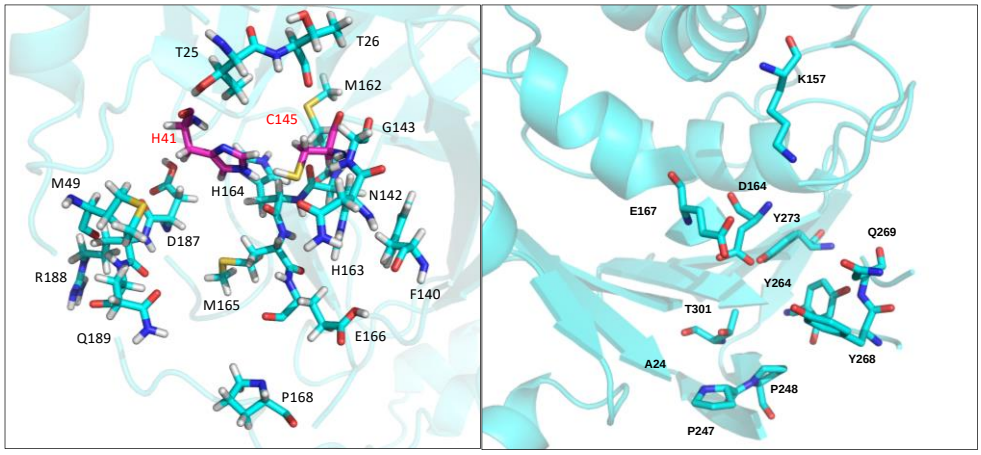

Figure S2 Active pockets of SARS-CoV-2 3CL^{pro} and PL^{pro}, including residues T25, T26, H41, C44, M49, F140, N142, G143, C145, M162, H163, H164, M165, E166, P168, D187, R188, Q189 and Q192 of 3CL^{pro}[6], and residues K157, D164, E167, A246, P247, P248, Y264, Y268, Q269, Y273 and T301 of PL^{pro}[10].

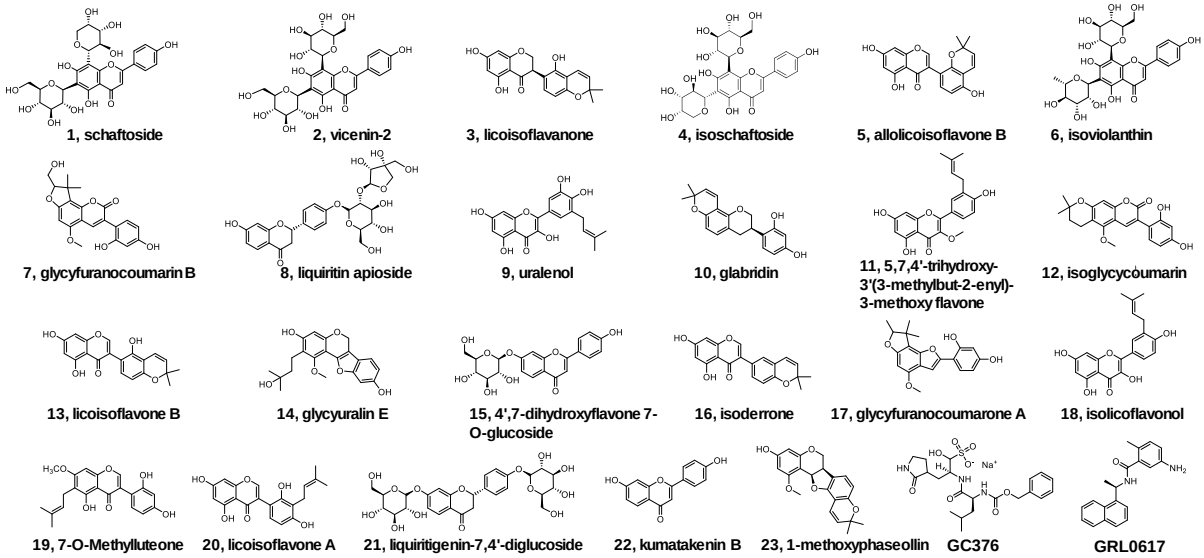

Figure S3 Structures of licorice hit compounds. **GC376** and **GLR0617** were used as the positive controls.

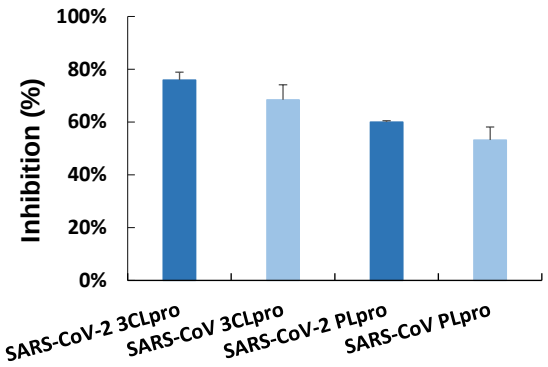

Figure S4 Inhibitory activities of schaftoside (8 μmol/L) against SARS-CoV-2 virus $3CL^{pro}$ and PL^{pro}, and SARS-CoV virus $3CL^{pro}$ and PL^{pro} (n = 3).

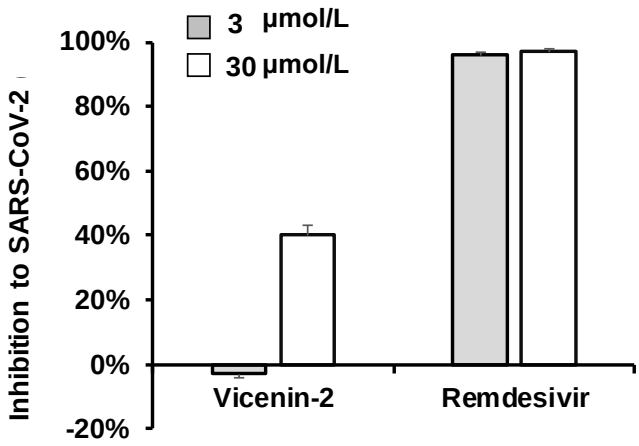

Figure S5 Inhibition of vicenin-2 against SARS-CoV-2 virus at 3 μmol/L and 30 μmol/L (n = 3). Remdesivir was used as the positive control.

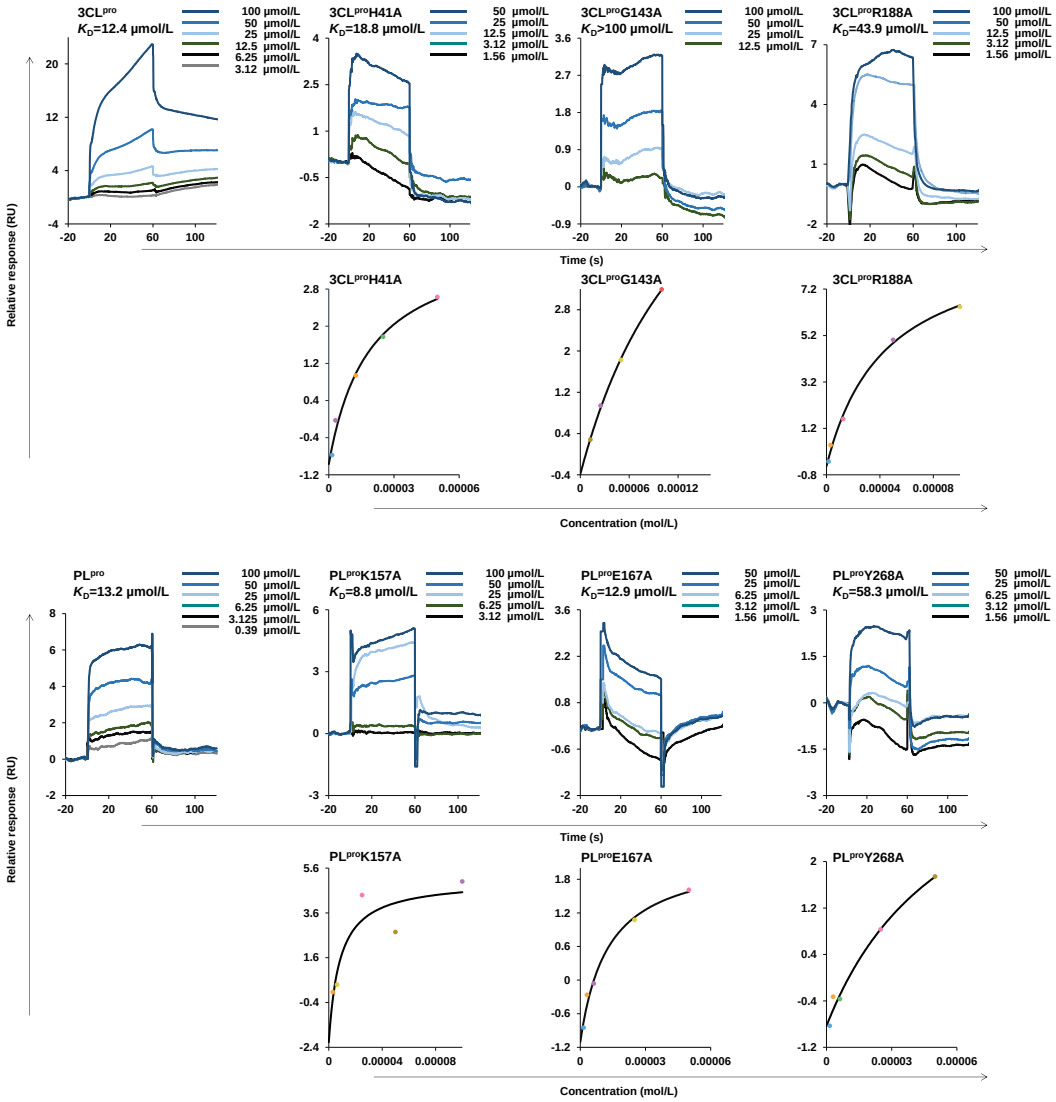

Figure S6 Relative responses of schaftoside to 3CL^{pro}, PL^{pro}, and their mutants determined by surface plasmon resonance. The measurements were performed using Biacore 8K.

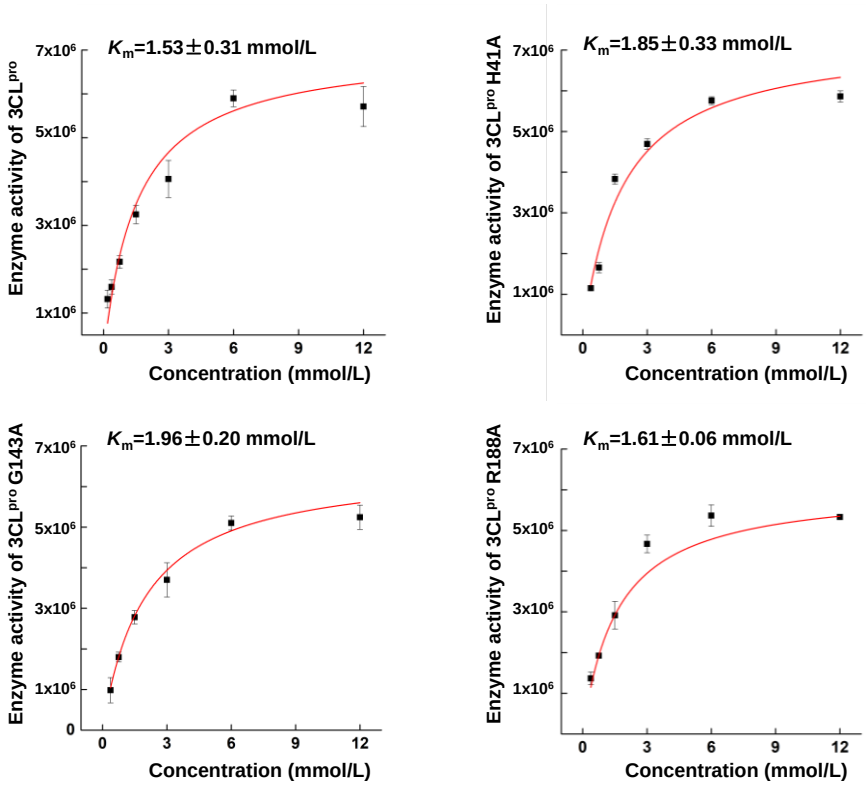

Figure S7 Enzyme activities of 3CL^{pro} and its mutants H41A, G143A, and R188A with 3CL^{pro} substrate at concentrations of 0.37, 0.75, 1.50, 3, 6 and 12 mmol/L, n = 3. Unit of enzyme activity: pmol/μg/min.

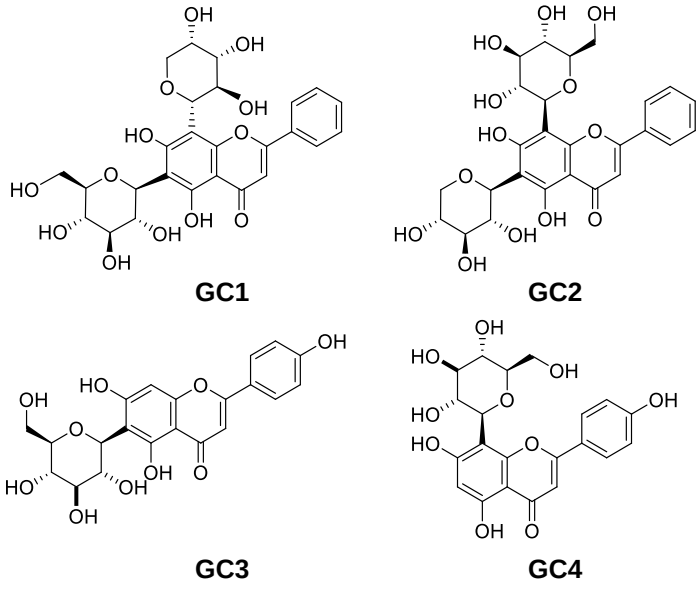

Figure S8 Structures of schaftoside analogues (flavonoid *C*-glycosides).

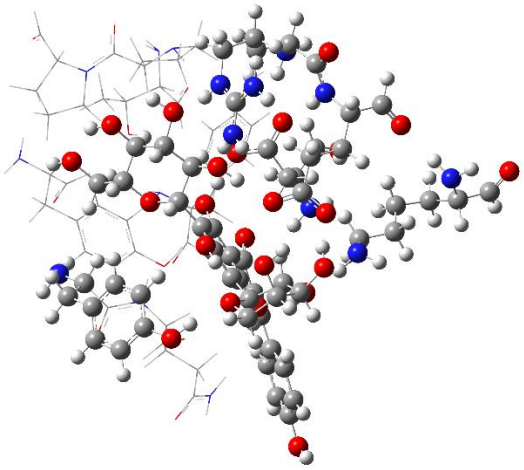

Figure S9 Molecular structure of schaftoside and residues of PL^{pro} determined by QM/MM calculations.

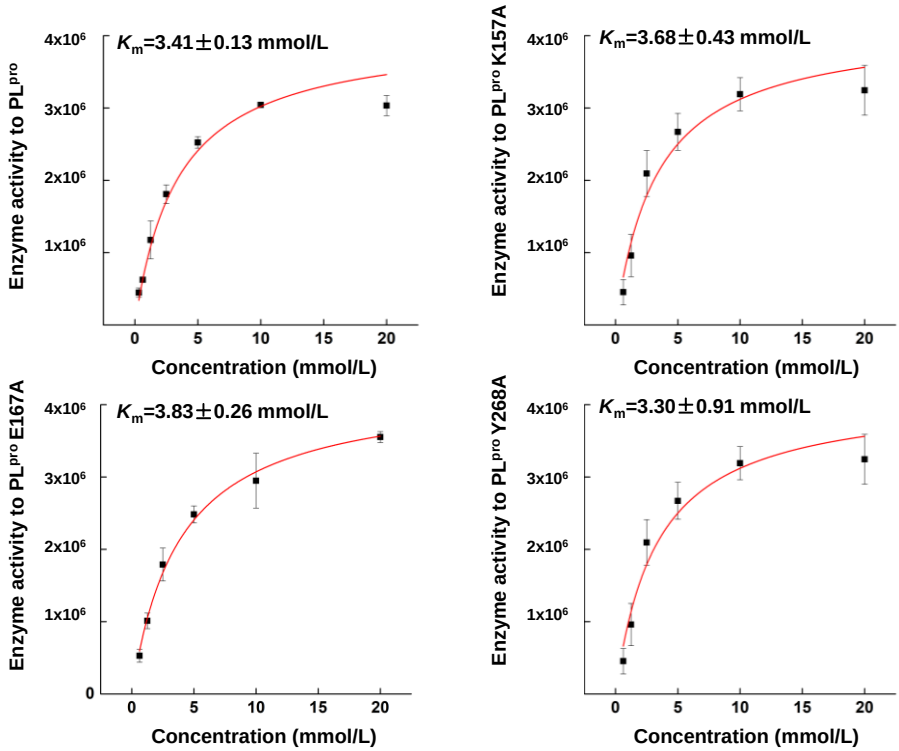

Figure S10 Enzyme activities of PL^{pro} and its mutants K157A, E167A, and Y268A with PL^{pro} substrate at concentrations of 0.625, 1.25, 2.5, 5, 10 and 20 mmol/L, n = 3. Unit of enzyme activity: pmol/μg/min.

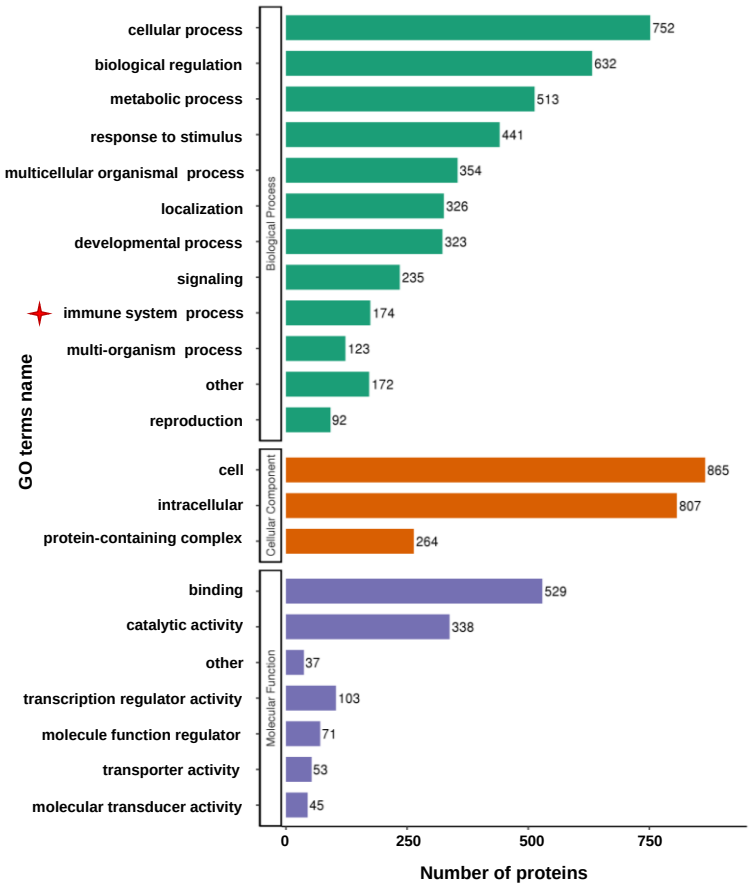

Figure S11 A list of up-regulated proteins upon treatment of schaftoside, performed by Gene Ontology (GO) annotation.

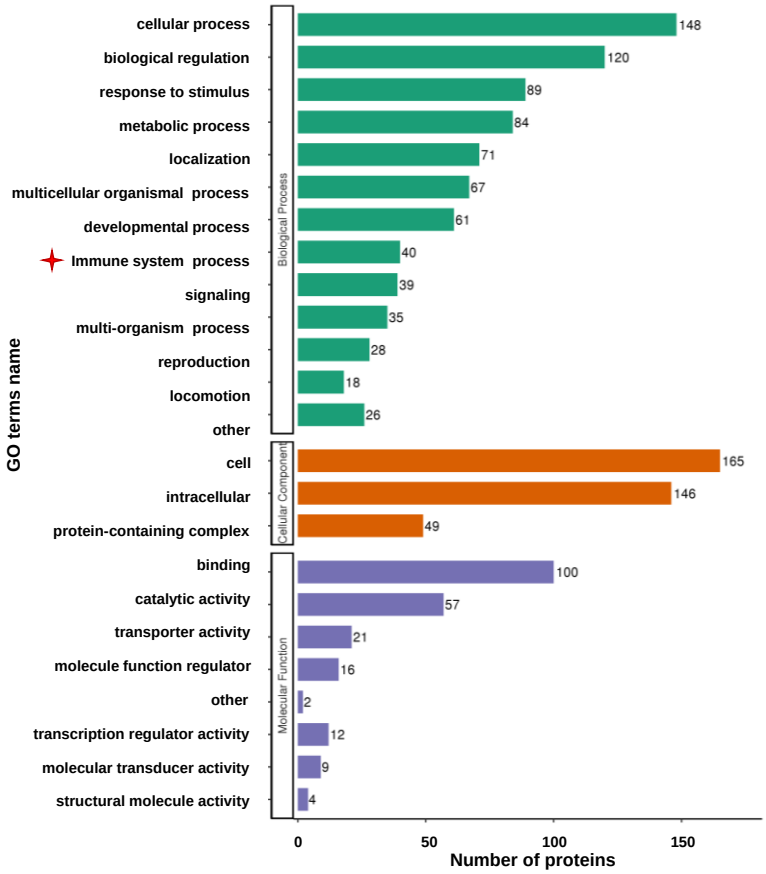

Figure S12 A list of down-regulated proteins upon treatment of schaftoside, performed by Gene Ontology (GO) annotation.

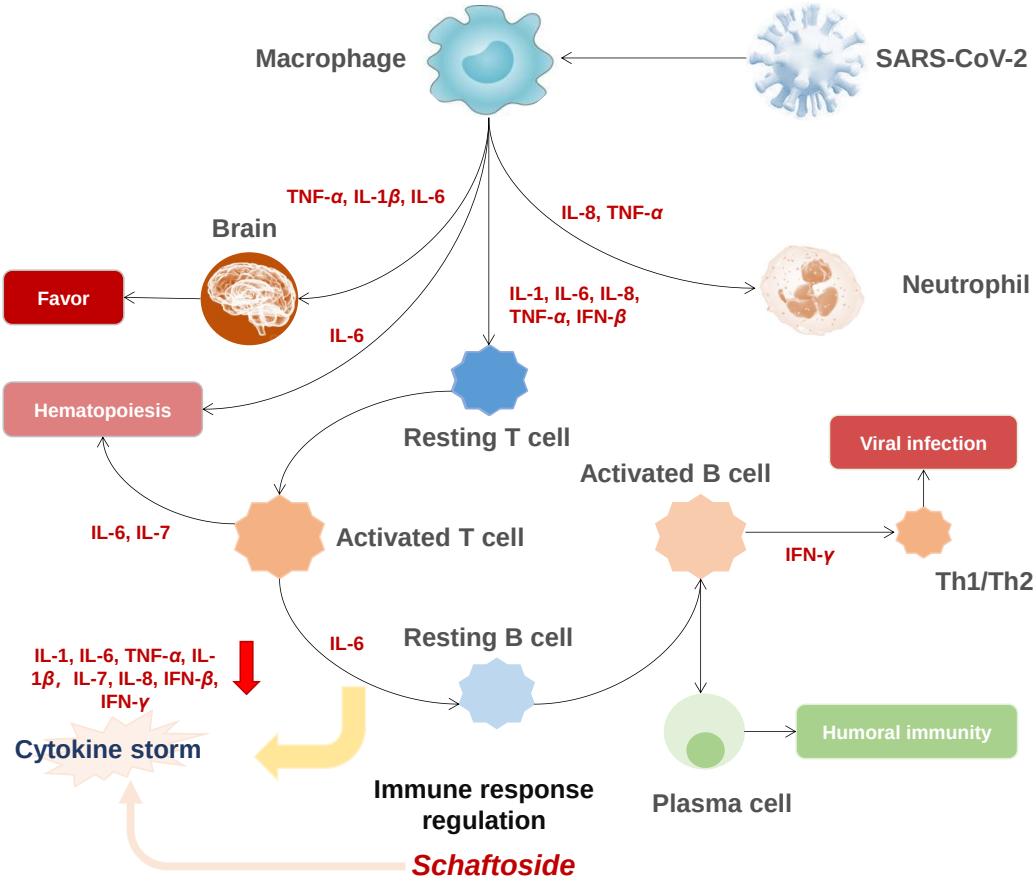

Figure S13 Proposed mechanisms of schaftoside to regulate immune response and inflammation of host cells[35-39].

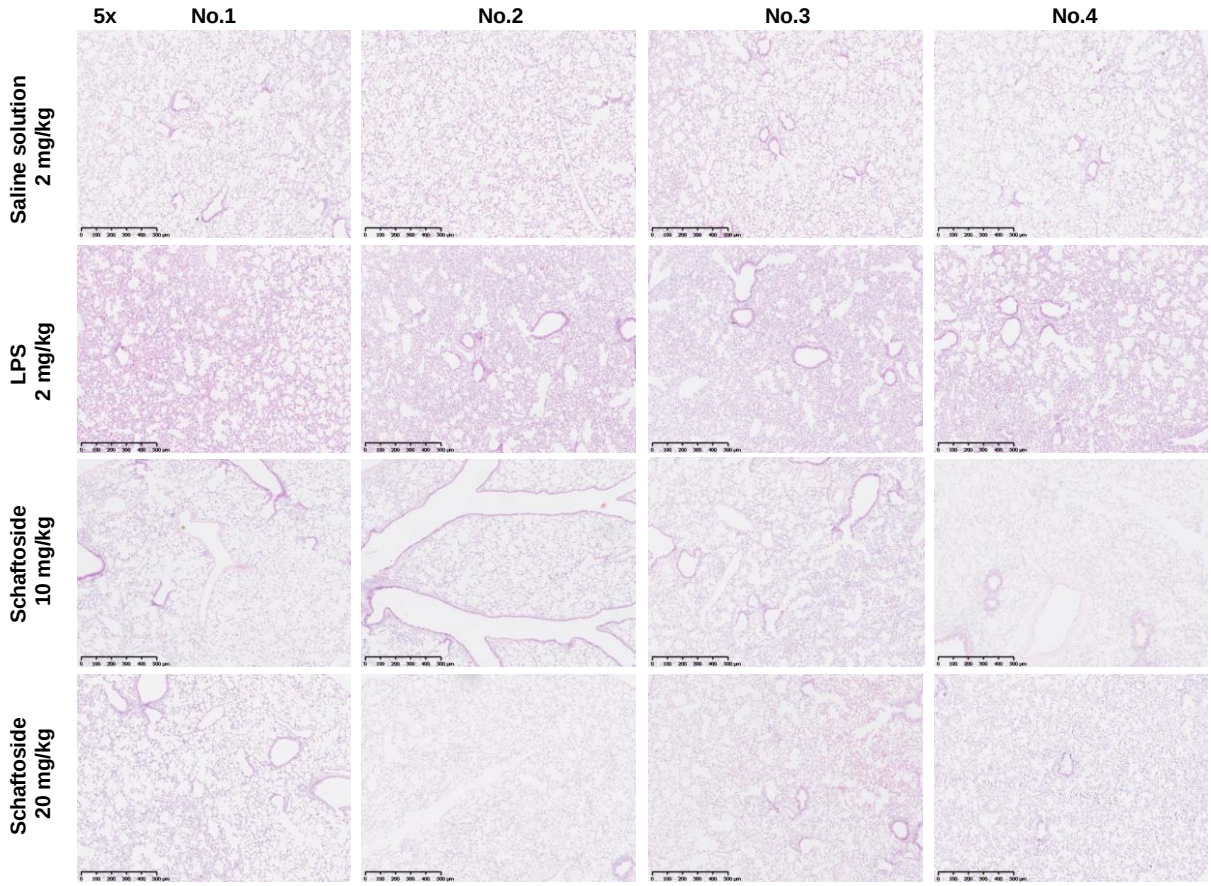

Figure S14 Effects of schaftoside (10 and 20 mg/kg, *i.g.*) on histological changes in LPS-induced ALI mice ($n = 4$, scale bar = 500 μm). Representative images of mice lung tissue stained using HE after 8 h of LPS treatment.

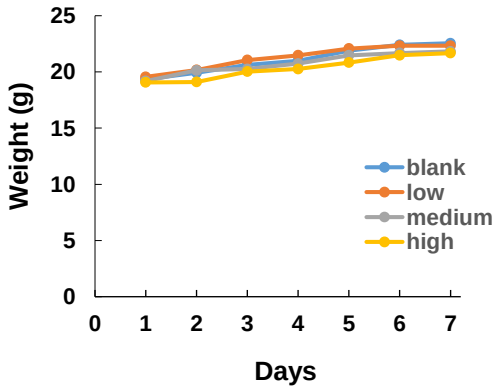

Figure S15 Weight of male ICR mice after schaftoside treatment in 7 days, $n = 5$. Four groups were divided, including blank (saline solution), low dose group (20 mg/kg, i.g.), medium dose group (40 mg/kg, i.g.), and high dose group (300 mg/kg, i.g.).

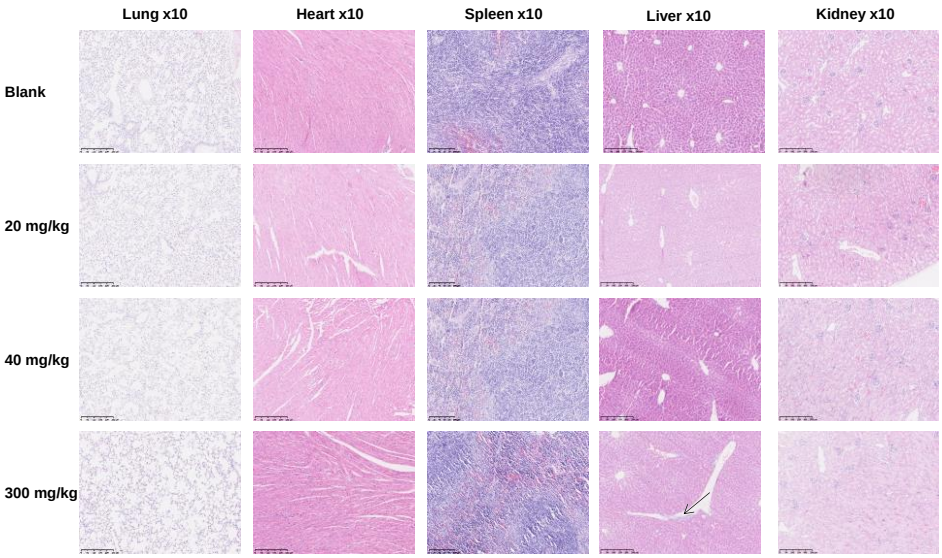

Figure S16 Effects of schaftoside on histological changes in different dosing groups (20 mg/kg, 40 mg/kg, and 300 mg/kg, *i.g.*) of male ICR mice. Blank, saline solution.

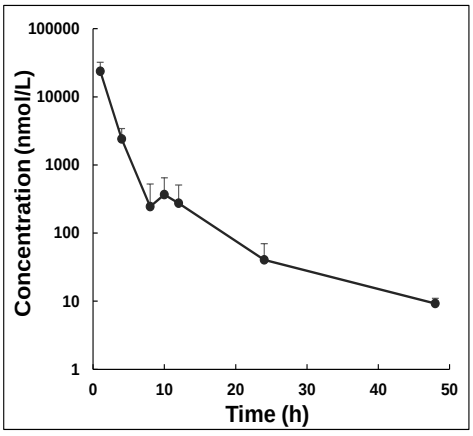

Figure S17 Time–plasma concentration curves of schaftoside in mice after intraperitoneal injection of schaftoside (150 mg/kg, i.p. T_{max}= 1 h, AUC_{total}= 0.026 h·g/L, $t_{1/2}$= 7.5 h, n = 4).

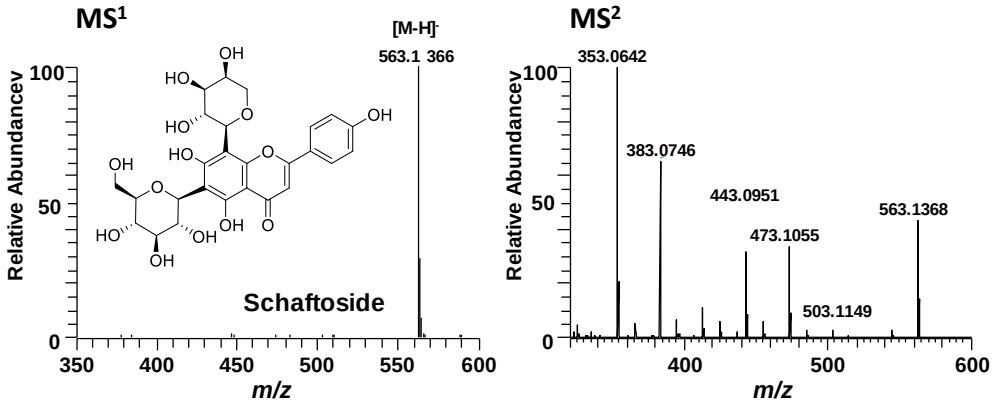

Figure S18 High-resolution MS and MS/MS spectra of schaftoside in the negative ion mode acquired on a Thermo Scientific Q-Exactive mass spectrometer (ThermoFisher). Data were processed using Xcalibur 4.1 software (ThermoFisher).

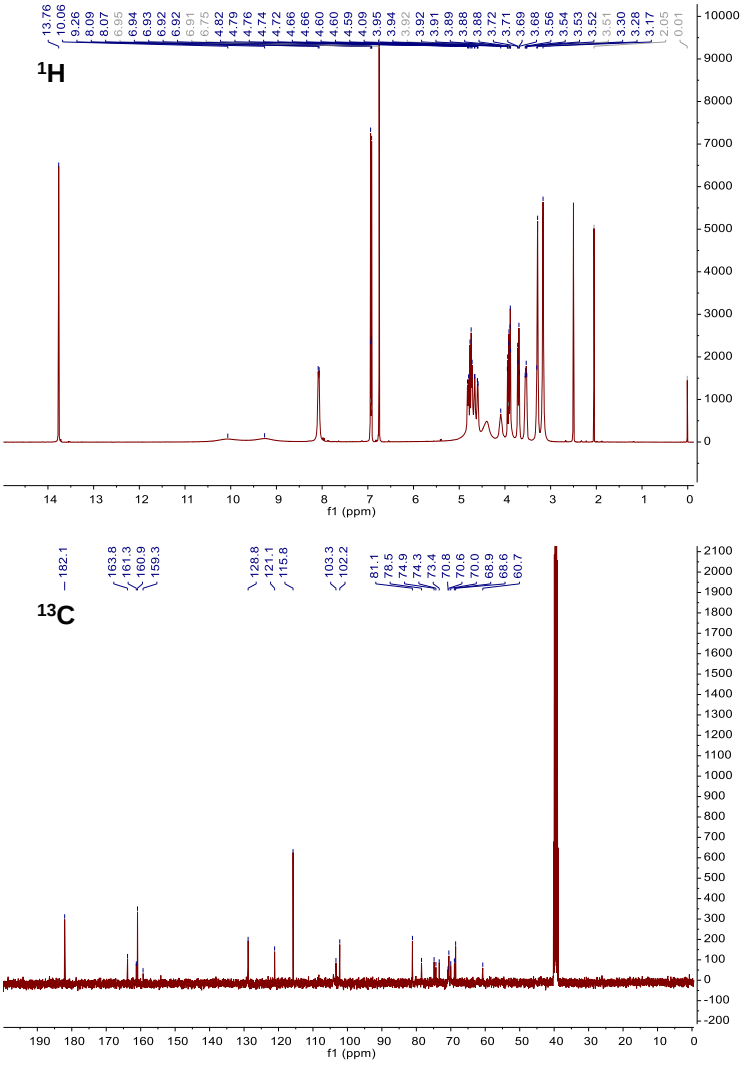

Figure S19 The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra of schaftoside in DMSO-d_6 at 60 °C.

4. Supporting tables

Table S1 Primers for site-directed mutagenesis.

Mutant	Sequence (5′→3′)
3CL^{pro} H41A,	CTGTCCAAGAGCAGTGATCTGCACCTCTGAAG
	TGCTCTTGGACAGTAAACTACGTCATCAAGCC
3CL^{pro} G143A	CATTCCTTAATGCATCATGTGGTAGTGTTG
	TGCATTAAGGAATGAACCCTTAATAGTGAAAT
3CL^{pro} R188A	CTTTTGTTGACGCACAAACAGCACAAGCAG
	TGCGTCAACAAAAGGTCCATAAAAGTTACCT
PL^{pro} K157A	CTGGCATATTGTAATGCAACCGTTGGTGAAC
	GCATTACAATATGCCAGAATCAGTGCACA
PL^{pro} E167A	CTGGGTGATGTGCGCGCAACCATGTCATATC
	GCGCGCACATCACCCAGTTCACCAACGGT
PL^{pro} Y268A	GAATATACCGGTAACGCACAGTGCGGCCAT
	TGCGTTACCGGTATATTCGCTTGCACAGGT

Table S2 The inhibitory activities against SARS-CoV-2 virus 3CL^{pro} of 12 traditional Chinese medicine herbs (50 μg/mL) and related single compounds (8 μmol/L).

No.	Name	Inhibition rate [%]
1	Isatidis Radix	38.17
2	Ephedrae Herba	37.76
3	Astragali Radix	34.70
4	Glycyrrhizae Radix et Rhizoma	32.85
5	Lonicerae Flos	25.47
6	Scutellariae Radix	24.81
7	Forsythiae Fructus	15.40
8	Platycodonis Radix	12.86
9	Semen Armeniacae Amarum	10.37
10	Rhizoma Atractylodis Macrocephalae	7.78
11	Herba Pogostemonis	0.00
12	Pericarpium Citri Reticulatae	0.00
13	schaftoside (**1**)	75.90
14	vicenin-2 (**2**)	76.53
15	licoisoflavanone (**3**)	66.86
16	isoschaftoside (**4**)	63.00
17	allolicoisoflavone B (**5**)	61.22
18	isoviolanthin (**6**)	37.84
19	glycyfuranocoumarin B (**7**)	27.67
20	liquiritin apioside (**8**)	27.35
21	uralenol (**9**)	21.24
22	glabridin (**10**)	17.43
23	5,7,4′-trihydroxy-3′(3-methylbut-2-enyl)-3-methoxy flavone (**11**)	16.92
24	isoglycycoumarin (**12**)	16.25
25	licoisoflavone B (**13**)	14.81
26	glycyuralin E (**14**)	13.61

27	4′,7-dihydroxyflavone 7-*O*-glucoside (**15**)	12.51
28	isoderrone (**16**)	11.77
29	glycyfuranocoumarone A (**17**)	5.90
30	GC1	46.12
31	GC2	41.93
32	GC3	38.81
33	GC4	15.27
34	**GC376**	82.29

GC376, positive control.

Table S3 The inhibitory activities against SARS-CoV-2 virus PL^{pro} of 12 traditional Chinese medicine herbs (50 μg/mL) and related single compounds (8 μmol/L).

No.	Name	Inhibition rate [%]
1	Herba Pogostemonis	43.76
2	Glycyrrhizae Radix et Rhizoma	40.93
3	Lonicerae Flos	38.45
4	Ephedrae Herba	32.63
5	Platycodonis Radix	35.71
6	Isatidis Radix	30.85
7	Pericarpium Citri Reticulatae	25.00
8	Scutellariae Radix	24.16
9	Semen Armeniacae Amarum	19.31
10	Rhizoma Atractylodis Macrocephalae	13.41
11	Forsythiae Fructus	12.09
12	Astragali Radix	3.62
13	schaftoside (**1**)	60.00
14	isolicoflavonol (**18**)	59.93
15	7-*O*-methylluteone (**19**)	54.30
16	licoisoflavone A (**20**)	45.50
17	liquiritigenin-7,4′-diglucoside (**21**)	42.76
18	kumatakenin B (**22**)	39.16
19	1-methoxyphaseollin (**23**)	34.95
20	**GRL0617**	84.75

GRL0617, positive control.

Table S4 Binding affinity of 125 licorice compounds with SARS-CoV-2 $3CL^{pro}$ by molecular docking.

No.	Name	Binding affinity [kcal/mol]
1	vicenin-2	-9.1
2	allolicoisoflavone B	-8.9
3	isoschaftoside	-8.7
4	isoderrone	-8.5
5	isoglycycoumarin	-8.5

6	schaftoside	-8.4
7	glycyfuranocoumarin B	-8.4
8	liquiritin apioside	-8.4
9	5,7,4′-trihydroxy-3′(3-methylbut-2-enyl)-3-methoxy flavone(5,7,4′-tr-3′(3-m-2-enyl)-3-methoxy flavone)	-8.3
10	isoviolanthin	-8.3
11	licoisoflavanone	-8.3
12	licoisoflavone B	-8.2
13	uralenol	-8.2
14	4′,7-dihydroxyflavone 7-*O*-glucoside	-8.2
15	glycyfuranocoumarin A	-8.1
16	glycyuralin E	-8.1
17	glabridin	-8.1
18	semilicoisoflavone B	-8.0
19	isoglycyrol	-8.0
20	IAA	-8.0
21	6,8-diprenylgenistein	-8.0
22	isolicoflavonol	-8.0
23	glycyfuranocoumarin C	-8.0
24	isolupalbigenin	-8.3
25	broussonol E	-8.0
26	glycyrol	-8.0
27	sophoraflavone B	-8.0
28	daidzin	-7.9
29	lupiwighteone	-7.9
30	1-methoxyphaseollin	-7.9
31	apigenin 6-*C*-rha-8-*C*-[6‴-(3-hydroxy-3-methylglutaroyl) -glucoside]	-7.8
32	isoliquiritin apioside	-7.8
33	neoliquiritin	-7.8
34	glycyuralin C	-7.8
35	topazolin	-7.8
36	glycyuralin D	-7.8
37	isoglabrone	-7.8
38	licocoumarone	-7.8
39	6-*C*-prenylorobol	-7.8
40	gancaonin L	-7.8
41	licoflavone A	-7.8
42	glycyuralin B	-7.7
43	glycyroside	-7.6
44	isoangustone A	-7.6
45	dehydroglyasperin D	-7.6
46	gancaonin I	-7.6
47	licoisoflavone A	-7.6
48	licoarylcoumarin	-7.6
49	pratensein	-7.6
50	dehydroglyasperin C	-7.6
51	kaempferol	-7.6
52	2′-hydroxyisolupalbigenin	-7.6
53	glycyrin	-7.6

54	glycyuralin A	-7.5
55	licoflavonol	-7.5
56	glyurallin A	-7.5
57	hirtellanine I	-7.5
58	glycyrrhiza-isoflavone C	-7.5
59	glycyuralin F	-7.5
60	liquiritin	-7.4
61	neoisoliquiritin	-7.4
62	genkwanin	-7.4
63	kumatakenin B	-7.4
64	luteone	-7.4
65	licoricidin	-7.4
66	5,5′,7-trihydroxy-2′,2′-dimethyl-2′*H*,4*H*-3,8′-bichromen-4-one	-7.4
67	glycycoumarin	-7.3
68	homobutein	-7.3
69	licochalcone A	-7.3
70	ononin	-7.2
71	isoliquiritin	-7.2
72	angustone A	-7.2
73	formononetin	-7.2
74	wighteone	-7.1
75	3-*O*-*β*-D-glucuronopyranosyl-glycyrrhetinic acid	-7.1
76	7-*O*-methylluteone	-7.1
77	licoricone	-7.1
78	7-methoxy-2′,4′-dihydroxy isoflavone	-7.1
79	11b-hydroxy-11b,1-dihydromedicarpin	-7.1
80	abiochanin A (Biochanin)	-7.1
81	3-methoxy-9-hydroxy-pterocarpan	-7.1
82	licorice-saponin B	-7.0
83	kaempferol-3-*O*-methyl ether	-7.0
84	isoliquiritigenin	-7.0
85	glyasperin C	-7.0
86	liquiritigenin-7,4′-diglucoside	-6.9
87	glucoliguiritin apioside	-6.9
88	glyasperin D	-6.9
89	kumatakenin	-6.9
90	genistein	-6.9
91	daidzein	-6.9
92	glycyrrhetinic acid	-6.8
93	echinatin	-6.8
94	syringic acid 4-*O*-glucopyranoside	-6.7
95	glicoricone	-6.7
96	glicophenone	-6.7
97	uralsaponin P	-6.6
98	isoliquiritigenin-4,4′-diglucoside	-6.5
99	licorice-saponin A3	-6.5
100	liquiritigenin	-6.4
101	licorice-saponin J2	-6.0
102	uralsaponin N	-5.9

103	uralsaponin W	-5.7
104	uralsaponin C	-5.6
105	uralsaponin Y	-5.6
106	licorice-saponin B2	-5.6
107	glycyrrhizic acid	-5.5
108	licorice-saponin H2	-5.5
109	araboglycyrrhizin	-5.5
110	uralsaponin Q	-5.3
111	uralsaponin V	-5.3
112	uralsaponin T	-5.1
113	3*β*-*O*-*β*-D-glucuronosyl-(1→2)-*β*-D-glucuronosyl-olean-9,12-diene-30-oic-acid	-5.1
114	licorice-saponin G2	-4.8
115	uralsaponin U	-4.8
116	22*β*-acetoxyl-glycyrrhaldehyde	-4.3
117	2-one-4-methoxy-pyran	-4.3
118	22*β*-acetoxylglycyrrhizin	-4.2
119	uralsaponin M	-4.2
120	licorice-saponin E2	-3.7
121	uralsaponin O	-3.7
122	uralsaponin R	-3.4
123	uralsaponin S	-3.4
124	uralsaponin F	-3.2
125	uralsaponin X	-2.1

Table S5 Binding affinity of 125 licorice compounds with SARS-CoV-2 PL^{pro} by molecular docking.

No.	Name	Binding affinity [kcal/mol]
1	liquiritigenin-7,4′-diglucoside	-8.5
2	schaftoside	-8.5
3	licoisoflavone A	-8.3
4	isolicoflavonol	-8.3
5	1-methoxyphaseollin	-8.3
6	7-*O*-methylluteone	-8.1
7	kumatakenin B	-8.1
8	glycycoumarin	-8.0
9	glycyfuranocoumarin C	-8.0
10	licoflavonol	-8.0
11	isolupalbigenin	-8.0
12	broussonol E	-8.0
13	licoflavone A	-8.0
14	topazolin	-8.0
15	licochalcone A	-8.0
16	glycyroside	-7.9
17	4′,7-dihydroxyflavone 7-*O*-glucoside	-7.9
18	licoisoflavanone	-7.9
19	semilicoisoflavone B	-7.9
20	uralenol	-7.9

21	homobutein	-7.9
22	angustone A	-7.8
23	genkwanin	-7.8
24	isoliquiritigenin	-7.8
25	liquiritigenin	-7.8
26	isoderrone	-7.8
27	apigenin 6-*C*-rha-8-*C*-[6‴-(3-hydroxy-3-methylglutaroyl)-glucopyranoside]	-7.7
28	daidzin	-7.7
29	glycyuralin A	-7.7
30	glycyuralin C	-7.7
31	luteone	-7.7
32	isoviolanthin	-7.6
33	liquiritin	-7.6
34	neoliquiritin	-7.6
35	IAA	-7.6
36	isoglycyrol	-7.6
37	wighteone	-7.6
38	allolicoisoflavone B	-7.6
39	glabridin	-7.6
40	licoricidin	-7.6
41	glycyrin	-7.6
42	isoliquiritin apioside	-7.5
43	isoliquiritin	-7.5
44	glycyrrhetinic acid	-7.5
45	5,5′,7-trihydroxy-2′,2′-dimethyl-2′*H*,4*H*-3,8′-bichromen-4-one	-7.5
46	glycyrol	-7.5
47	gancaonin I	-7.5
48	echinatin	-7.5
49	glycyuralin F	-7.5
50	2′-hydroxyisolupalbigenin	-7.5
51	isoschaftoside	-7.4
52	neoisoliquiritin	-7.4
53	sophoraflavone B	-7.4
54	glycyfuranocoumarone A	-7.4
55	glyurallin A	-7.4
56	licocoumarone	-7.4
57	6-*C*-prenylorobol	-7.4
58	licorice-saponin B	-7.3
59	glyasperin D	-7.3
60	dehydroglyasperin D	-7.3
61	dehydroglyasperin C	-7.3
62	isoliquiritigenin-4,4′-diglucoside	-7.2
63	liquiritin apioside	-7.2
64	5,7,4′-trihydroxy-3′(3-methylbut-2-enyl)-3-methoxy flavone (5,7,4′-tr-3′(3-m-2-enyl)-3-methoxy flavone)	-7.2
65	isoglabrone	-7.2
66	11b-hydroxy-11b,1-dihydromedicarpin	-7.2
67	glicoricone	-7.2
68	glyasperin C	-7.2

69	6,8-diprenylgenistein	-7.2
70	ononin	-7.1
71	licorice-saponin J2	-7.1
72	uralsaponin V	-7.1
73	glycyuralin B	-7.1
74	lupiwighteone	-7.1
75	glycyuralin E	-7.1
76	licorice-saponin E2	-7.0
77	uralsaponin O	-7.0
78	glycyrrhizic acid	-7.0
79	isoglycycoumarin	-7.0
80	glycyfuranocoumarin B	-7.0
81	pratensein	-7.0
82	gancaonin L	-7.0
83	3-methoxy-9-hydroxy-pterocarpan	-7.0
84	glicophenone	-7.0
85	licoisoflavone B	-7.0
86	syringic acid 4-*O*-glucopyranoside	-6.9
87	uralsaponin C	-6.9
88	licorice-saponin G2	-6.9
89	uralsaponin U	-6.9
90	glycyuralin D	-6.9
91	kaempferol-3-*O*-methyl ether	-6.9
92	glycyrrhiza-isoflavone C	-6.9
93	abiochanin A (Biochanin)	-6.9
94	glycyfuranocoumarin A	-6.8
95	7-methoxy-2′,4′-dihydroxy isoflavone	-6.8
96	glucoliguiritin apioside	-6.7
97	uralsaponin N	-6.7
98	licorice-saponin H2	-6.7
99	araboglycyrrhizin	-6.7
100	3*β*-*O*-[*β*-D-glucuronopyranosyl-(1→2)-*β*-D-glucuronopyranosyl]-olean-9,12-diene-30-oic-acid	-6.7
101	uralsaponin W	-6.7
102	formononetin	-6.7
103	genistein	-6.7
104	kaempferol	-6.7
105	daidzein	-6.7
106	vicenin-2	-6.5
107	kumatakenin	-6.5
108	licoarylcoumarin	-6.5
109	licorice-saponin A3	-6.4
110	uralsaponin Y	-6.4
111	3-*O*-*β*-D-glucuronopyranosyl-glycyrrhetinic acid	-6.0
112	licoricone	-5.9
113	Hirtellanine I	-5.9
114	uralsaponin T	-5.8
115	uralsaponin P	-5.8
116	uralsaponin R	-5.7
117	uralsaponin S	-5.7

118	licorice-saponin B2	-5.7
119	22β-acetoxylglycyrrhizin	-5.5
120	uralsaponin M	-5.5
121	uralsaponin F	-5.4
122	22β-acetoxyl-glycyrrhaldehyde	-5.4
123	uralsaponin Q	-4.9
124	2-one-4-methoxy-pyran	-4.6
125	uralsaponin X	-4.4

Table S6 Crystallographic data collection and refinement statistics.

Crystallographic data	$3CL^{pro}$
space group	*I*121
a, *b*, *c* (Å)	44.7, 53.5, 113.5
α, β, γ (°)	90.0, 101.2, 90.0
resolution (Å)	13.09-2.08(2.14-2.08)
No. of measured reflections	104103 (8669）
No. of unique reflections	15801 (1298)
completeness (%)	99.2 (98.8)
multiplicity	6.6 (6.7)
<*I*/d(*I*)>	15.7 (3.2)
R_{merge} (%)	8.5 (48.2)
R_{work} (%)	21.2
R_{free} (%)	29.2
*R*msd bond lengths (Å)	0.01
*R*msd bond angles (°)	0.94
B-factors	21.8
Ramachandran plot residues in favored regions (%)	96.27
PDB ID	7V7M

Table S7 Proteins related with immune response and inflammation determined by GO enrichment.

No.	GO Terms	Description	Fold Enrichment	Fisher's exact test *P* value	Protein accession	Protein description	Gene name	sch/ck Ratio
1	down-regulated	leukocyte migration	4.34	4.04276E-05	A0A0D9R9X4	Fibronectin OS=Chlorocebus sabaeus OX=60711 GN=FN1 PE=4 SV=1	Fibronectin 1 (*FN1*)	0.633
2			4.34	4.04276E-05	A0A0D9S645	Lymphocyte function-associated antigen 3 isoform 1(predicted) OS=Chlorocebus sabaeus OX=60711 GN=CD58 PE=4 SV=1	CD58 Molecule (*CD58*)	0.766
3			4.34	4.04276E-05	A0A0D9QZF5	CD44 antigen OS=Chlorocebus sabaeus OX=60711 GN=CD44 PE=4 SV=1	CD44 Molecule (*CD44*)	0.755
4			4.34	4.04276E-05	A0A0D9S0W4	Cystine/glutamate transporter(predicted) OS=Chlorocebus sabaeus OX=60711 GN=SLC7A11 PE=3 SV=1	Solute Carrier Family 7 Member 11 (*SLC7A11*)	0.655
5			4.34	4.04276E-05	A0A0D9S1V7	ZnMc domain-containing protein OS=Chlorocebus sabaeus OX=60711 GN=MMP1 PE=3 SV=1	Matrix Metallopeptidase 1 (*MMP1*)	0.581
6			4.34	4.04276E-05	A0A0D9R354	Solute carrier family 3 member 2 OS=Chlorocebus sabaeus OX=60711 GN=SLC3A2 PE=4 SV=1	Solute Carrier Family 3 Member 2 (*SLC3A2*)	0.575
7			4.34	4.04276E-05	A0A0D9R3G8	Neural cell adhesion molecule L1 isoform 1(predicted) OS=Chlorocebus sabaeus OX=60711 GN=L1CAM PE=3 SV=1	L1 Cell Adhesion Molecule (*L1CAM*)	0.767
8			4.34	4.04276E-05	A0A0D9R703	Vitellogenin domain-containing protein OS=Chlorocebus sabaeus OX=60711 GN=APOB PE=4 SV=1	Apolipoprotein B (*APOB*)	0.556
9			4.34	4.04276E-05	A0A0D9REC3	Tyrosine-protein phosphatase non-receptor type substrate 1(predicted) OS=Chlorocebus sabaeus OX=60711 PE=4 SV=1	_	0.707

10			4.34	4.04276E-05	A0A0D9S232	Large neutral amino acids transporter small subunit 1(predicted) OS=Chlorocebus sabaeus OX=60711 GN=SLC7A5 PE=3 SV=1	Solute Carrier Family 7 Member 5 (*SLC7A5*)	0.6
11			4.34	4.04276E-05	A0A0D9QUZ5	Integrin beta OS=Chlorocebus sabaeus OX=60711 PE=3 SV=1	_	0.6
12		neutrophil mediated immunity	1.79	8.05358E-06	A0A0D9R6H0	Maltase-glucoamylase, intestinal(predicted) OS=Chlorocebus sabaeus OX=60711 GN=MGAM PE=3 SV=1	Maltase-Glucoamylase (*MGAM*)	2.445
13	up-regulated		1.79	8.05358E-06	A0A0D9RI88	Ribonuclease T2(predicted) OS=Chlorocebus sabaeus OX=60711 PE=3 SV=1	_	1.829
14			1.79	8.05358E-06	A0A0D9RK06	Phospholipase OS=Chlorocebus sabaeus OX=60711 GN=PLD1 PE=3 SV=1	Phospholipase D1 (*PLD1*)	1.575
15			1.79	8.05358E-06	A0A0D9RWL1	Cathepsin B OS=Chlorocebus sabaeus OX=60711 GN=CTSB PE=3 SV=1	Cathepsin B (*CTSB*)	1.452
16			1.79	8.05358E-06	A0A0D9RCE1	Isocitrate dehydrogenase [NADP] OS=Chlorocebus sabaeus OX=60711 GN=IDH1 PE=3 SV=1	Isocitrate Dehydrogenase (NADP(+)) 1 (*IDH1*)	1.455
17			1.79	8.05358E-06	A0A0D9RC57	CUE domain-containing protein OS=Chlorocebus sabaeus OX=60711 GN=TOLLIP PE=3 SV=1	Toll Interacting Protein (*TOLLIP*)	1.434
18			1.79	8.05358E-06	A0A0D9R8S1	Aldehyde dehydrogenase OS=Chlorocebus sabaeus OX=60711 PE=3 SV=1	_	1.367
19			1.79	8.05358E-06	A0A0D9S0V3	Granulins(predicted) OS=Chlorocebus sabaeus OX=60711 GN=GRN PE=3 SV=1	Granulin Precursor (*GRN*)	2.532
20			1.79	8.05358E-06	A0A0D9RPV3	Syntenin-1 isoform 3(predicted) OS=Chlorocebus sabaeus OX=60711 PE=4 SV=1	_	1.537
21			1.79	8.05358E-06	A0A0D9RZ27	NHL repeat-containing protein 3(predicted) OS=Chlorocebus sabaeus OX=60711	NHL Repeat Containing 3	1.352

				GN=NHLRC3 PE=4 SV=1	(*NHLRC3*)	
22	1.79	8.05358E-06	A0A0D9QVL6	Beta-mannosidase OS=Chlorocebus sabaeus OX=60711 GN=MANBA PE=3 SV=1	Mannosidase Beta (*MANBA*)	1.426
23	1.79	8.05358E-06	A0A0D9S3B0	SGNH_hydro domain-containing protein OS=Chlorocebus sabaeus OX=60711 GN=PAFAH1B2 PE=4 SV=1	Platelet Activating Factor Acetylhydrolase 1b Catalytic Subunit 2 (*PAFAH1B2*)	1.36
24	1.79	8.05358E-06	A0A0D9RST9	Cathepsin X OS=Chlorocebus sabaeus OX=60711 GN=CTSZ PE=3 SV=1	Cathepsin Z (*CTSZ*)	1.304
25	1.79	8.05358E-06	A0A0D9R7Z3	Prosaposin OS=Chlorocebus sabaeus OX=60711 GN=PSAP PE=4 SV=1	Prosaposin (*PSAP*)	1.511
26	1.79	8.05358E-06	A0A0D9RRW7	Sulfatase domain-containing protein OS=Chlorocebus sabaeus OX=60711 GN=ARSB PE=3 SV=1	Arylsulfatase B (*ARSB*)	2.106
27	1.79	8.05358E-06	A0A0D9QZJ6	COMM domain-containing protein OS=Chlorocebus sabaeus OX=60711 GN=COMMD9 PE=4 SV=1	COMM Domain Containing 9 (*COMMD9*)	1.308
28	1.79	8.05358E-06	A0A0D9REY5	GM2 ganglioside activator OS=Chlorocebus sabaeus OX=60711 GN=GM2A PE=4 SV=1	GM2 Ganglioside Activator (*GM2A*)	1.906
29	1.79	8.05358E-06	A0A0D9RVU7	CN hydrolase domain-containing protein OS=Chlorocebus sabaeus OX=60711 GN=VNN1 PE=3 SV=1	Vanin 1 (*VNN1*)	5.144
30	1.79	8.05358E-06	A0A0D9S4B2	P-type domain-containing protein OS=Chlorocebus sabaeus OX=60711 GN=GAA PE=3 SV=1	Alpha Glucosidase (*GAA*)	1.591
31	1.79	8.05358E-06	A0A0D9RSR2	Grancalcin(predicted) OS=Chlorocebus sabaeus OX=60711 GN=GCA PE=4 SV=1	Grancalcin (*GCA*)	1.338
32	1.79	8.05358E-06	A0A0D9R149	Nitrilase family member 2 OS=Chlorocebus	Nitrilase Family	1.39

					sabaeus OX=60711 GN=NIT2 PE=4 SV=1	Member 2 (*NIT2*)	
33		1.79	8.05358E-06	A0A0D9RVB6	Dipeptidyl peptidase 2 preproprotein(predicted) OS=Chlorocebus sabaeus OX=60711 GN=DPP7 PE=3 SV=1	Dipeptidyl Peptidase 7 (*DPP7*)	2.447
34		1.79	8.05358E-06	A0A0D9S372	ORM1-like protein OS=Chlorocebus sabaeus OX=60711 GN=ORMDL3 PE=3 SV=1	ORMDL Sphingolipid Biosynthesis Regulator 3 (*ORMDL3*)	1.473
35		1.79	8.05358E-06	A0A0D9RNP1	ADP-ribosylation factor-like 8A, isoform CRA_a(predicted) OS=Chlorocebus sabaeus OX=60711 GN=ARL8A PE=3 SV=1	ADP Ribosylation Factor Like GTPase 8A (*ARL8A*)	1.397
36		1.79	8.05358E-06	A0A0D9R6W4	Ig-like domain-containing protein OS=Chlorocebus sabaeus OX=60711 PE=3 SV=1	_	1.721
37		1.79	8.05358E-06	A0A0D9RC71	DSN1 component of MIS12 kinetochore complex OS=Chlorocebus sabaeus OX=60711 GN=DSN1 PE=4 SV=1	DSN1 Component Of MIS12 Kinetochore Complex (*DSN1*)	1.482
38	regulation of leukocyte activation	1.43	0.04257892	A0A0D9R8A5	Dedicator of cytokinesis protein 8(predicted) OS=Chlorocebus sabaeus OX=60711 GN=DOCK8 PE=3 SV=1	Dedicator Of Cytokinesis 8 (*DOCK8*)	1.308
39		1.43	0.04257892	A0A0D9RVU7	CN hydrolase domain-containing protein OS=Chlorocebus sabaeus OX=60711 GN=VNN1 PE=3 SV=1	Vanin 1 (*VNN1*)	5.144
40		1.43	0.04257892	A0A0D9SBP1	Major prion protein OS=Chlorocebus sabaeus OX=60711 GN=PRNP PE=3 SV=1	Prion Protein (*PRNP*)	1.365
41		1.43	0.04257892	A0A0D9RMV2	Zinc finger and BTB domain-containing protein	Zinc Finger And	1.48

				1 isoform 2(predicted) OS=Chlorocebus sabaeus OX=60711 GN=ZBTB1 PE=4 SV=1	BTB Domain Containing 1 (*ZBTB1*)	
42	1.43	0.04257892	A0A0D9R6W4	Ig-like domain-containing protein OS=Chlorocebus sabaeus OX=60711 PE=3 SV=1	_	1.721
43	1.43	0.04257892	A0A0D9RPX9	C2H2-type domain-containing protein OS=Chlorocebus sabaeus OX=60711 GN=ZNF608 PE=4 SV=1	Zinc Finger Protein 608 (*ZNF608*)	1.658
44	1.43	0.04257892	A0A0D9S5B6	ZBTB7B isoform 2(predicted) OS=Chlorocebus sabaeus OX=60711 GN=ZBTB7B PE=4 SV=1	Zinc Finger And BTB Domain Containing 7B (*ZBTB7B*)	1.443
45	1.43	0.04257892	A0A0D9RNB6	PKD domain-containing protein OS=Chlorocebus sabaeus OX=60711 GN=GPNMB PE=4 SV=1	Glycoprotein Nmb (*GPNMB*)	2.249
46	1.43	0.04257892	A0A0D9RTD5	RPN13_C domain-containing protein OS=Chlorocebus sabaeus OX=60711 GN=ADRM1 PE=3 SV=1	ADRM1 26S Proteasome Ubiquitin Receptor (*ADRM1*)	1.526
47	1.43	0.04257892	A0A0D9RTH5	RING-CH-type domain-containing protein OS=Chlorocebus sabaeus OX=60711 GN=MARCHF7 PE=4 SV=1	Membrane Associated Ring-CH-Type Finger 7 (*MARCHF7*)	1.313
48	1.43	0.04257892	A0A0D9RCQ5	Tyrosine-protein phosphatase non-receptor type OS=Chlorocebus sabaeus OX=60711 GN=PTPN6 PE=3 SV=1	Protein Tyrosine Phosphatase Non-Receptor Type 6 (*PTPN6*)	1.338
49	1.43	0.04257892	A0A0D9RIY8	Nedd4 family interacting protein 1(predicted)	Nedd4 Family	1.302

				OS=Chlorocebus sabaeus OX=60711 GN=NDFIP1 PE=4 SV=1	Interacting Protein 1 (*NDFIP1*)	
50	1.43	0.04257892	A0A0D9S385	FA complementation group A OS=Chlorocebus sabaeus OX=60711 GN=FANCA PE=4 SV=1	FA Complementation Group A (*FANCA*)	1.438
51	1.43	0.04257892	A0A0D9RPF5	Syndecan OS=Chlorocebus sabaeus OX=60711 GN=SDC4 PE=3 SV=1	Syndecan 4 (*SDC4*)	
52	1.43	0.04257892	A0A0D9RHA5	Ephrin RBD domain-containing protein OS=Chlorocebus sabaeus OX=60711 GN=EFNB1 PE=3 SV=1	Ephrin B1 (*EFNB1*)	
53	1.43	0.04257892	A0A0D9RAN9	Ig-like domain-containing protein OS=Chlorocebus sabaeus OX=60711 PE=4 SV=1	_	
54	1.43	0.04257892	A0A0D9RL01	ZFP36 ring finger protein like 1(predicted) OS=Chlorocebus sabaeus OX=60711 GN=ZFP36L1 PE=4 SV=1	ZFP36 Ring Finger Protein Like 1 (*ZFP36L1*)	
55	1.43	0.04257892	A0A0D9RNY8	Adenosine deaminase OS=Chlorocebus sabaeus OX=60711 PE=3 SV=1	_	
56	1.43	0.04257892	A0A0D9RPF5	Syndecan OS=Chlorocebus sabaeus OX=60711 GN=SDC4 PE=3 SV=1	Syndecan 4 (*SDC4*)	1.366
57	1.43	0.04257892	A0A0D9RHA5	Ephrin RBD domain-containing protein OS=Chlorocebus sabaeus OX=60711 GN=EFNB1 PE=3 SV=1	Ephrin B1 (*EFNB1*)	1.363
58	1.43	0.04257892	A0A0D9RAN9	Ig-like domain-containing protein OS=Chlorocebus sabaeus OX=60711 PE=4 SV=1	_	1.557
59	1.43	0.04257892	A0A0D9RL01	ZFP36 ring finger protein like 1(predicted) OS=Chlorocebus sabaeus OX=60711 GN=ZFP36L1 PE=4 SV=1	ZFP36 Ring Finger Protein Like 1 (*ZFP36L1*)	1.564

60		1.43	0.04257892	A0A0D9RNY8	Adenosine deaminase OS=Chlorocebus sabaeus OX=60711 PE=3 SV=1	_	1.529
61		1.43	0.04257892	A0A0D9RPF5	Syndecan OS=Chlorocebus sabaeus OX=60711 GN=SDC4 PE=3 SV=1	Syndecan 4 (*SDC4*)	1.366
62		1.43	0.04257892	A0A0D9RHA5	Ephrin RBD domain-containing protein OS=Chlorocebus sabaeus OX=60711 GN=EFNB1 PE=3 SV=1	Ephrin B1 (*EFNB1*)	1.363
63		1.43	0.04257892	A0A0D9RAN9	Ig-like domain-containing protein OS=Chlorocebus sabaeus OX=60711 PE=4 SV=1	_	1.557
64		1.43	0.04257892	A0A0D9RL01	ZFP36 ring finger protein like 1(predicted) OS=Chlorocebus sabaeus OX=60711 GN=ZFP36L1 PE=4 SV=1	ZFP36 Ring Finger Protein Like 1 (*ZFP36L1*)	1.564
65		1.43	0.04257892	A0A0D9RNY8	Adenosine deaminase OS=Chlorocebus sabaeus OX=60711 PE=3 SV=1	_	1.529
66		1.43	0.04257892	A0A0D9RPF5	Syndecan OS=Chlorocebus sabaeus OX=60711 GN=SDC4 PE=3 SV=1	Syndecan 4 (*SDC4*)	1.366
67	positive regulation of	2.25	0.043744343	A0A0D9S8W1	Protein kinase C OS=Chlorocebus sabaeus OX=60711 GN=PRKCZ PE=3 SV=1	Protein Kinase C Zeta (*PRKCZ*)	2.645
68	T cell differentiation	2.25	0.043744343	A0A0D9RBA8	TGF-beta receptor type-2 OS=Chlorocebus sabaeus OX=60711 GN=TGFBR2 PE=3 SV=1	Transforming Growth Factor Beta Receptor 2 (*TGFBR2*)	1.36
69		2.25	0.043744343	A0A0D9RVU7	CN hydrolase domain-containing protein OS=Chlorocebus sabaeus OX=60711 GN=VNN1 PE=3 SV=1	Vanin 1 (*VNN1*)	5.144
70		2.25	0.043744343	A0A0D9RMV2	Zinc finger and BTB domain-containing protein 1 isoform 2(predicted) OS=Chlorocebus sabaeus OX=60711 GN=ZBTB1 PE=4 SV=1	Zinc Finger And BTB Domain Containing 1 (*ZBTB1*)	1.48

71		2.25	0.043744343	A0A0D9S5B6	ZBTB7B isoform 2(predicted) OS=Chlorocebus sabaeus OX=60711 GN=ZBTB7B PE=4 SV=1	Zinc Finger And BTB Domain Containing 7B (*ZBTB7B*)	1.443
72	immune response	1.44	0.000385524	A0A0D9RI88	Ribonuclease T2(predicted) OS=Chlorocebus sabaeus OX=60711 PE=3 SV=1	_	1.829
73		1.44	0.000385524	A0A0D9R6H0	Maltase-glucoamylase, intestinal(predicted) OS=Chlorocebus sabaeus OX=60711 GN=MGAM PE=3 SV=1	Maltase-Glucoamylase (*MGAM*)	2.445
74		1.44	0.000385524	A0A0D9RK06	Phospholipase OS=Chlorocebus sabaeus OX=60711 GN=PLD1 PE=3 SV=1	Phospholipase D1 (PLD1)	1.575
75		1.44	0.000385524	A0A0D9RWL1	Cathepsin B OS=Chlorocebus sabaeus OX=60711 GN=CTSB PE=3 SV=1	Cathepsin B (*CTSB*)	1.452
76		1.44	0.000385524	A0A0D9RRW7	Sulfatase domain-containing protein OS=Chlorocebus sabaeus OX=60711 GN=ARSB PE=3 SV=1	Arylsulfatase B (*ARSB*)	2.106
77		1.44	0.000385524	A0A0D9QZJ6	COMM domain-containing protein OS=Chlorocebus sabaeus OX=60711 GN=COMMD9 PE=4 SV=1	COMM Domain Containing 9 (*COMMD9*)	1.308
78		1.44	0.000385524	A0A0D9RC71	DSN1 component of MIS12 kinetochore complex OS=Chlorocebus sabaeus OX=60711 GN=DSN1 PE=4 SV=1	DSN1 Component Of MIS12 Kinetochore Complex (*DSN1*)	1.482
79		1.44	0.000385524	A0A0D9REY5	GM2 ganglioside activator OS=Chlorocebus sabaeus OX=60711 GN=GM2A PE=4 SV=1	GM2 Ganglioside Activator (*GM2A*)	1.906
80		1.44	0.000385524	A0A0D9RVU7	CN hydrolase domain-containing protein OS=Chlorocebus sabaeus OX=60711 GN=VNN1 PE=3 SV=1	Vanin 1 (*VNN1*)	5.144
81		1.44	0.000385524	A0A0D9S4B2	P-type domain-containing protein	Alpha	1.591

				OS=Chlorocebus sabaeus OX=60711 GN=GAA PE=3 SV=1	Glucosidase (*GAA*)	
82	1.44	0.000385524	A0A0D9RB33	Ig-like domain-containing protein OS=Chlorocebus sabaeus OX=60711 GN=TAPBP PE=4 SV=1	TAP Binding Protein (*TAPBP*)	1.646
83	1.44	0.000385524	A0A0D9RSR2	Grancalcin(predicted) OS=Chlorocebus sabaeus OX=60711 GN=GCA PE=4 SV=1	Grancalcin (*GCA*)	1.338
84	1.44	0.000385524	A0A0D9RTW6	Clusterin OS=Chlorocebus sabaeus OX=60711 GN=CLU PE=3 SV=1	Clusterin (*CLU*)	1.439
85	1.44	0.000385524	A0A0D9R149	Nitrilase family member 2 OS=Chlorocebus sabaeus OX=60711 GN=NIT2 PE=4 SV=1	Member 2 (*NIT2*)	1.39
86	1.44	0.000385524	A0A0D9S372	ORM1-like protein OS=Chlorocebus sabaeus OX=60711 GN=ORMDL3 PE=3 SV=1	ORMDL Sphingolipid Biosynthesis Regulator 3 (*ORMDL3*)	1.473
87	1.44	0.000385524	A0A0D9RNP1	ADP-ribosylation factor-like 8A, isoform CRA_a(predicted) OS=Chlorocebus sabaeus OX=60711 GN=ARL8A PE=3 SV=1	ADP Ribosylation Factor Like GTPase 8A (*ARL8A*)	1.397
88	1.44	0.000385524	A0A0D9RAI2	LIM zinc-binding domain-containing protein OS=Chlorocebus sabaeus OX=60711 PE=4 SV=1	_	2.133
89	1.44	0.000385524	A0A0D9QZB2	Gamma-interferon-inducible lysosomal thiol reductase preproprotein(predicted) OS=Chlorocebus sabaeus OX=60711 GN=IFI30 PE=3 SV=1	IFI30 Lysosomal Thiol Reductase (*IFI30*)	1.687
90	1.44	0.000385524	A0A0D9R167	B cell linker OS=Chlorocebus sabaeus OX=60711 GN=BLNK PE=4 SV=1	B Cell Linker (BLNK)	1.652
91	1.44	0.000385524	A0A0D9R6W4	Ig-like domain-containing protein	_	1.721

				OS=Chlorocebus sabaeus OX=60711 PE=3 SV=1		
92	1.44	0.000385524	A0A0D9S4W5	Junctional adhesion molecule 3 OS=Chlorocebus sabaeus OX=60711 GN=JAM3 PE=4 SV=1	Junctional Adhesion Molecule 3 (JAM3)	1.424
93	1.44	0.000385524	A0A0D9RC57	CUE domain-containing protein OS=Chlorocebus sabaeus OX=60711 GN=TOLLIP PE=3 SV=1	Toll Interacting Protein (*TOLLIP*)	1.434
94	1.44	0.000385524	A0A0D9RCE1	Isocitrate dehydrogenase [NADP] OS=Chlorocebus sabaeus OX=60711 GN=IDH1 PE=3 SV=1	Isocitrate Dehydrogenase (NADP(+)) 1 (*IDH1*)	1.455
95	1.44	0.000385524	A0A0D9RVB6	Dipeptidyl peptidase 2 preproprotein(predicted) OS=Chlorocebus sabaeus OX=60711 GN=DPP7 PE=3 SV=1	Dipeptidyl Peptidase 7 (*DPP7*)	2.447
96	1.44	0.000385524	A0A0D9R7Z3	Prosaposin OS=Chlorocebus sabaeus OX=60711 GN=PSAP PE=4 SV=1	Prosaposin (*PSAP*)	1.511