Supplementary Table 1. Interactions of flavonoids from propolis and bee honey with host-cell receptors proteins of SARS-CoV-2

Proteins (PDB ID)	Compounds	Binding energy (kcal/mol)	Main interactions	References
ACE-II (1R4L)	MLN-4760*▲	-7.28	Tyr127, Arg273, Phe274, Trp271, Arg273, Phe274, His345, Pro346, Cys361, Thr371, His374, Glu375, His378, Glu406, Phe504, His505, Tyr515, Arg518	[1]
ACE-II (1R4L)	Rutin	-8.98	HB (Asn149, His345, Asp269, Glu375, Glu406, Thr371, Tyr127, Asp368), PC (Arg273), PPT (His374), Al (Cys344), PAl (Tyr 127) Tyr127, Ser128, Leu144, Glu145, Asn149, Asp269, Met270, Trp271, Arg273, Phe274, Val343, Cys344, His345, Pro346, Met360, Cys361, Lys363, Asp367, Asp368, Thr371, His374, Glu375, Glu406, Phe504, Arg518 ▲	[1]
ACE-II (1R4L)	CAPE▲	-7.76	Tyr127, Ser128, Leu144, Glu145, Asn149, Trp271, Val343, Cys344, His345, Pro346, Met360, Cys361, Thr362, Lys363, Asp368, Phe504	[1]
ACE-II (1R4L)	Myricetin▲	-7.70	Arg273, Phe274, His345, Pro346, Thr347, Ala348, Thr371, His374, Glu375, His378, Glu406, Phe504, His505, Tyr515, Arg518	[1]
ACE-II (1R4L)	Quercetin▲	-7.62	Arg273, Phe274, His345, Pro346, Thr347, Ala348, Thr371, Glu375, His374, His378, Glu406, Phe504, His505, Tyr515, Arg518	[1]

Proteins (PDB ID)	Compounds	Binding energy (kcal/mol)	Main interactions	References
ACE-II (1R4L)	Pinocembrin▲	-7.46	Tyr127, Ser128, Leu144, Glu145, Asn149, Trp271, Val343, Cys344, His345, Pro346, Met360, Cys361, Thr362, Lys363, Asp368	[1]
ACE-II (1R4L)	Hesperetin▲	-7.40	Arg273, His345, Pro346, Thr347, Ala348, Trp349, Thr371, His374, Glu375, His378, Glu406, Phe504, His505, Tyr510, Tyr515, Arg518	[1]
ACE-II (1R4L)	Galangin▲	-7.18	Arg273, Phe274, His345, Pro346, Thr347, Ala348, Thr371, His374, Glu375, His378, Glu406, Phe504, His505, Tyr515, Arg518	[1]
ACE-II (1R4L)	Chrysin▲	-7.08	Tyr127, Ser128, Glu145, Asn149, Cys344, His345, Pro346, Met360, Cys361, Thr362, Lys363, Asp368, Phe504	[1]
ACE-II (1R4L)	Luteolin▲	-6.93	Arg273, Phe274, His345, Pro346, Thr347, Ala348, Trp349, His374, Glu375, His378, Asp382, Glu402, Phe504, His505, Tyr510, Tyr515, Arg518	[1]
ACE-II (1R4L)	Caffeic acid▲	-5.53	Arg273, His345, Pro346, Thr347, Ala348, His374, Glu375, His378, Phe504, His505, Tyr515	[1]
TMPRSS2 (O15393)	Camostat mesylate *	-5.90	HB (Gly464), PP (Val275, Gln276, Val278, Val 280, His296, Cys297, Leu302, Asp435, Ser436, Cys437, Gln438, Gly439,	[2]

Proteins (PDB ID)	Compounds	Binding energy (kcal/mol)	Main interactions	References
			Ser441, Thr459, Trp461, Gly462, Cys465, Ala466, Gly472, Val473)	
TMPRSS2 (O15393)	CAPE	-6.20	HB (Gly464, Ser436), PP (Cys281, Val280, His296, Cys297, Glu299, Leu302, Asp435, Cys437, Gln438, Gly439, Asp440, Ser441, Thr459, Ser460, Trp461, Gly462, Cys465	[2]
S1 subunit (6m0j)	**Dexamethasone***	−7.9		[3]
S1 subunit (6m0j)	**Naringin**	−9.8	HB (Asp367, Thr371, Lys441, Ser409, Glu406) hydrophobic (Asn290, Ile291, His374, Leu370, Leu410, Ala413, Pro415, Phe438, Gln442)	[3]
S1 subunit (6m0j)	**Rutin**	−9.2	NR	
S1 subunit (6m0j)	**Galangin**	−8.2	NR	
S1 subunit (6m0j)	**Quercetin**	−8.2	NR	
S1 subunit (6m0j)	**Chrysin**	−8.1	NR	
S1 subunit (6m0j)	**Luteolin**	−8.0	NR	
S1 subunit (7BZ5)	Remdesivir*	−165.9◎	3HB (Arg509, Asn343, Ala344)	[4]
S1 subunit (7BZ5)	Avigan*	−46.3◎	3HB (Arg509)	[4]
S1 subunit (7BZ5)	Hydroxychloroquine*	−79.8◎	2HB (Arg509)	[4]

Proteins (PDB ID)	Compounds	Binding energy (kcal/mol)	Main interactions	References
S1 subunit (7BZ5)	Rutin	−94.3◎	1HB (Glu484)	[4]
S1 subunit (7BZ5)	CAPE	−77.8◎	2HB (Asn437, Ala372)	[4]
S1 subunit (7BZ5)	Pinobanksin	−77.4◎	3HB (Trp436, Phe342)	[4]
S1 subunit (7BZ5)	Quercetin	−67.8◎	2HB (Gln474)	[4]
S1 subunit (7BZ5)	Chrysin	−66.2◎	1HB (Asn343)	[4]
S1 subunit (7BZ5)	Kaempferol	−62.3◎	2HB (Trp436)	[4]
S1 subunit (7BZ5)	Pinocembrin	−60.5◎	1HB (Gly482)	[4]
S1 subunit (7BZ5)	Galangin	−59.5◎	1HB (Gly482)	[4]
S1 subunit (7BZ5)	P-coumaric acid	−56.5◎	3HB (Arg509, Ser373)	[4]
PP2A-B56 (5SWF-A)	^{293}LDPLSE^{298}◆	-4.9	Leu296 formed HB with the hydrophobic pocket, and Glu298 formed ionic bonds with amino acid residues in the positively-charged region in PP2A B56. ○	[5]
PP2A-B56 (5SWF-A)	Artepillin C	-6.1	The two prenyl groups of artepillin C were docked into the same two pockets as in ^{293}LDPLSE^{298}; however, only through HB. ○	{Maaroufi, 2020 #1892
Mpro (6YNQ)	Remdesivir*	– 8.6	HB (Glu A: 166, His A: 41, Thr A: 25) PA (Pro A: 168)	[6]

Proteins (PDB ID)	Compounds	Binding energy (kcal/mol)	Main interactions	References
Mpro (6YNQ)	Rutin	− 8.7	HB (CYS A: 145, HIS A: 163, SER A: 46, THR A: 45, HIS A: 41, GLU A: 166, And GLN A: 189) Van der Waals (Asn A: 142.) PA (Met A: 49)	[6]
Mpro (6Y2F)	13b*	−8.2	HB (His41, Gly143, Ser144, Cys145, Glu166) HDPC (Thr25, Cys44, Met49, Leu141, Asn142, His163, His164, Met165, Leu167, Asp187, Gln189)	[7]
Mpro (6Y2F)	14b*	−7.2	HB (Phe140, Glu166) HDPC (His41, Met49, Leu141, Asn142, His163, His164, Met165, Leu167, Pro168, Asp187, Arg188, Gln189)	[7]
Mpro (6Y2F)	Broussoflavonol F	−7.8	HB (Gly143, Ser144, Cys145) HDPC (Thr26, His41, Met49, Leu141, Asn142, His163, His164, Met165, Glu166, Arg188, Gln189)	[7]
Mpro (6Y2F)	Glyasperin A	−7.8	HB (Thr25, His164, Arg188) HDPC (His41, Cys145, Met165, Glu166, Val186, Asp187, Gln189, Thr190, Gln192)	[7]
Mpro (6Y2F)	Sulabiroins A	−7.6	HB (Glu166) HDPC (His41, Asn142, His164, Met165, Asp187, Arg188, Gln189)	[7]
RdRp(7M71)	Theaflavin*	-11.2	HB (Ala550, Trp617, Aap623, Asp760, Glu811), PA (Asp760, Asp761), PAl (Ala550, Cys622)	[8]
RdRp(7M71)	Rutin	-11.7	HB (Tyr619, Lys621, Asp760, Glu811), PA (Glu811)	[8]

Proteins (PDB ID)	Compounds	Binding energy (kcal/mol)	Main interactions	References
RdRp(7M71)	Quercetin-7-O-glucuronide	-10.5	HB (Arg553, Ser549, Tyr619, Trp800, Glu811, Cys813), PC (ARG555, LYS551)	[8]
RdRp(7M71)	Quercetin-3'-O-glucuronide	-10.5	HB (Cys622, Asp623, Asp760, Glu811, Cys813, Ser814), PA (Asp618, Asp761)	[8]
RdRp(7M71)	Quercetin-3-O-glucuronide	-10.2	HB (Thr556, Tyr619, Lys621, Thr687, Asn691, Ser759, Asp760), PC (Arg555, Arg553), PA (Asp623), PAl (Lys621)	[8]
RdRp(7M71)	Quercetin-7-O-sulfate	-9.4	HB (Lys545, Lys621, Arg624), PC (Arg555, Arg553), PA (Asp623), PAl (Arg624)	[8]
RdRp(7M71)	Quercetin-3-O-sulfate	-8.8	HB (Asp452, Arg553, Thr556, Tyr619), PC (Arg553), PA (Asp623)	[8]
RdRp(7M71)	Quercetin-3'-O-sulfate	-8.8	HB (Ser814), PA (Asp760, Asp761)	[8]
RdRp(7M71)	Quercetin	-8.2	HB (Asp760, Trp800), PA (Asp761)	[8]
RdRp(7M71)	Nicotiflorin	-11.3	HB (Tyr619, Lus621, Asp760), PA (Glu811)	[8]
RdRp(7M71)	Kaempferol-4'-O-glucuronide	-10.2	HB (Asp618, Lys621, Asp623, Asp761), PA (Glu811)	[8]
RdRp(7M71)	Kaempferol-3-O-glucuronide	-10.1	HB (Tyr619, Asp760, Asp761, Glu811, Cys813)	[8]

Proteins (PDB ID)	Compounds	Binding energy (kcal/mol)	Main interactions	References
RdRp(7M71)	Kaempferol-7-O-glucuronide	-10.0	HB (Asp760, Trp800), PA (Glu811), PAl (Lys798)	[8]
RdRp(7M71)	Kaempferol-7-O-sulfate	-9.3	HB (Lys545, Lys621, Arg624), PC (Arg553, Arg555), PA (Asp623), PAl (Arg624)	[8]
RdRp(7M71)	Kaempferol-4'-O-sulfate	-9.2	HB (Arg553, Lys621, Thr687, Asn691), PC (Arg553), PA (Asp623), PS (Cys622), PAl (Lys621)	[8]
RdRp(7M71)	Kaempferol-3-O-sulfate	-8.7	HB (Arg553, Arg555, Thr556, Tyr619, Lys621, Arg624), PC (Arg553), PA (Asp623), PAl (Lys621)	[8]
RdRp(7M71)	Kaempferol	-7.7	HB (Tyr619, Ser814), PA (Asp760, Asp761)	[8]
3CLpro(6W63)	x77*	-12.4	HB (Gly143, Glu166), PS (Met49), PAl (Leu27, His41, Pro168), PAm (Leu141)	[8]
3CLpro(6W63)	Rutin	-10.3	HB (Asn142, Asp187), PS (Cys145, Met165), PP (His41), PC (His41), PAl (Cys44, Met49, Cys145)	[8]
3CLpro(6W63)	Quercetin-7-O-glucuronide	-10.9	HB (Thr26, Glu166, Gln189), PP (His41), PC (His41), PAl (Met49)	[8]
3CLpro(6W63)	Quercetin-3'-O-glucuronide	-10.2	HB (Gly143, His164), PAl (Met49)	[8]

Proteins (PDB ID)	Compounds	Binding energy (kcal/mol)	Main interactions	References
3CLpro(6W63)	Quercetin-3-O-glucuronide	-10.7	HB (Thr25, Cys44, Asn142, Ser144, His163, Met165, Glu166, Arg188), PAl (Met49, Met165)	[8]
3CLpro(6W63)	Quercetin-7-O-sulfate	-9.5	HB (Thr25, Ser144, Glu166), PS (Cys145), PC (His41), PAl (Met49, Met165)	[8]
3CLpro(6W63)	Quercetin-3-O-sulfate	-9.5	HB (Asn142, Thr190), PS (Met165), Psi (Gln189), PAl (Met165)	[8]
3CLpro(6W63)	Quercetin-3'-O-sulfate	-9.2	HB (Met49, Gly143, Asp187), Psi (Thr25), PP (His41), PC (His41), PAl (Cys44, Met49)	[8]
3CLpro(6W63)	Quercetin	-8.3	HB (Glu166), PS (Met49), PC (His41), PAl (Met165)	[8]
3CLpro(6W63)	Nicotiflorin	-11.2	HB (Asn142, Asp187), PP (His41), PS (Cys145), PC (His41), PAl (Cys44, Met49, Cys145)	[8]
3CLpro(6W63)	Kaempferol-7-O-glucuronide	-10.9	HB (Thr24, Asp187), PP(His41), PS(Cys145), PC (His41), PAl (Cys44, Met49, Cys145)	[8]
3CLpro(6W63)	Kaempferol-4'-O-glucuronide	-9.7	HB (Thr24, Cys44), PS(Met49), PP(His41), PAl (Cys44, Met49)	[8]
3CLpro(6W63)	Kaempferol-3-O-glucuronide	-9.1	HB (Asn142, Glu166), PP (His41), PC(His41), PAl (Cys44, Met49)	[8]
3CLpro(6W63)	Kaempferol-7-O-sulfate	-9.1	HB (Gly143, Glu166) ,PS (Cys145), PP (His41), PC (His41), PAl (Cys44, Met49, Cys145)	[8]

Proteins (PDB ID)	Compounds	Binding energy (kcal/mol)	Main interactions	References
3CLpro(6W63)	Kaempferol-4'-O-sulfate	-9.0	HB (Leu141, His163), PS (Cys145), PP (His41)	[8]
3CLpro(6W63)	Kaempferol-3-O-sulfate	-9.4	HB (Met49, His41, Gly143, Glu166), PS (Cys44, Met49, Cys145), PP (His41), PC (His41), PAl (Cys145)	[8]
3CLpro(6W63)	Kaempferol	-8.1	HB (Met49, Gly143, Asp187), PS (Cys44, Cys145), PP (His41), PC (His41), PAl (Cys145)	[8]
3CLpro(6LU7)	N3*	−133.6◎	5HB (Gly71, Lys97, Gly11, Glu14)	[4]
3CLpro(6LU7)	Remdesivir*	−136.4◎	10HB (Gln110, Thr111, Thr292, Phe294, Asp153, Ser158)	[4]
3CLpro(6LU7)	Avigan*	−33.3◎	6HB (Gln110, Thr111, Thr292, Asn151, Asp295)	[4]
3CLpro(6LU7)	Hydroxychloroquine*	−65.9◎	3HB (Gln110, Thr111, Thr292)	[4]
3CLpro(6LU7)	Rutin	−92.8◎	18HB (Lys102, Gln110, Asn151, Ser158, Thr111, Ile152, Asp153)	[4]
3CLpro(6LU7)	CAPE	−67.8◎	5HB (Lys102, Asp153)	[4]
3CLpro(6LU7)	Quercetin	−57.5◎	10HB (Lys102, Gln110, Thr111, Asp153, Asp295)	[4]
3CLpro(6LU7)	Kaempferol	−56.3◎	7HB (Lys5, Lys137, Tyr239, Glu288, Glu290)	[4]
3CLpro(6LU7)	Pinocembrin	−56.2◎	3HB (Gly71, N119, Ser121)	[4]

Proteins (PDB ID)	Compounds	Binding energy (kcal/mol)	Main interactions	References
3CLpro(6LU7)	Pinobanksin	−54.1◎	5HB (Gln110, Thr111, Ser158)	[4]
3CLpro(6LU7)	Galangin	−53.2◎	4HB (Gly71, Glu14, Gly15, Ser121)	[4]
3CLpro(6LU7)	Chrysin	−52.9◎	8HB (Lys102, Gln110, Thr111, S158, Asp295)	[4]
3CLpro(6LU7)	P-Coumaric acid	−45.5◎	5HB (Thr111, Thr292, Ser158)	[4]
3CLpro(6LU7)	Benzoic acid	−35.4◎	4HB (Gln110, Thr111)	[4]
Mpro (5R7Y)	3-phenyllactic acid	-5.867	HB (GLN-189), PP(HIE-41)	[8]
Mpro (5R7Y)	Caffeic acid	-4.387	HB (GLN-189, HIE-164)	[8]
Mpro (5R7Y)	CAPE	-6.386	HB (THR-24, THR-26), PP(HIE-41)	[8]
Mpro (5R7Y)	Chrysin	-6.097	HB (SER-46, THR-24, THR-26), PP(HIE-41)	[8]
Mpro (5R7Y)	Galangin	-6.307	HB (SER-46, THR-24) , PP(HIE-41)	[8]

* Reference compound; ◎ affinity of binding is expressed as Molsoft Internal Coordinate Mechanics (ICM) score; ▲ reports on the nature of binding interactions are missing; ◆ a motif in S1 subdomain of spike protein; ○ the study did not state amino acid residues in PP2A B56 that were involved in the interactions with ^{293}LDPLSE^{298} and artepillin C. **Abbreviations:** ACE-II: angiotensin-converting enzyme-related carboxypeptidase; PP2A-B56: B56 regulatory unit of phosphatase 2A; TMPRSS2: transmembrane protease serine 2; 3CLpro/Mpro: chymotrypsin-like protease/main protease; RdRp: RNA-dependent RNA polymerase; CAPE: caffeic acid phenethyl ester; MLN-4760: ((S,S)-2-1-Carboxy-2-[3-(3,5-Dıchloro-Benzyl)-3h-Imıdazol-4-Yl]-Ethylamıno-4-Methyl-Pentanoic Acid); HB: hydrogen bond; PS: π-sulfur; PA: π-anion; PC: π-cation; PP: π-π; AL: alkyl; PAl: π-alkyl; PPT: π-π T shape; Psi: π-sigma; PAm: π-amide; HDPC: hydrophobic interactions that were not specified.

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