Epicatechin as a potential hit to target ERK2 in breast cancer: molecular docking, molecular dynamic simulation studies

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SUPPLEMENTARY MATERIAL

Table S1: Phytochemicals that failed to dock in the binding pocket of ERK2 protein.

S. No.	Phytochemical	Smiles
1	4-terpinol	CC(C)[C@]1(O)CCC(C)CC1
2	8-Oxyberberine	O1COC(C2)C1CC(CC3)C2C(N34)CC5C(C4O)C(OC)C(OC)CC5
3	9-epoxylignan	C1CC(O)C(OC)CC1C[C@H](CO[C@@H]2OC)[C@@H]2CC3CC(OC)C(O)CC3
4	Allicin	CCCS(O)SCCC
5	Anisaldehyde	COC1CCC(CC1)CO
6	Apigenin-7-O-glucoside	O[C@H]1[C@H](O)[C@@H](CO)O[C@H]([C@@H]1O)OC(C2)CC(O)C(C23)C(O)CC(O3)C4CCC(O)CC4
7	Apigenin-7-O-glucuronide	O[C@@H]1[C@@H](C(O)O)O[C@H]([C@H](O)[C@H]1O)OC(C2)CC(O)C(C23)C(O)CC(O3)C4CCC(O)CC4
8	Armatamide	O1COC(C12)CCC(C2)CCC(O)NCCC3CCC(OC)CC3

9	Ascorbic acid	OC[C@H](O)[C@H]1OC(O)C(O)C1O
10	Berbamine	CN1CCC(C2[C@H]13)CC(OC)C(OC)C2OC4CC5[C@@H](N(C)CCC5CC4OC)CC6CCC(CC6)OC7CC(C3)CCC7O
11	Berberine	O1COC(C2)C1CC(CC3)C2C(N34)CC5C(C4)C(OC)C(OC)CC5
12	Bergapten	C1COC(C12)CC3C(C2OC)CCC(O3)O
13	Bornyl acetate	OC(C)O[C@@H]1C[C@H](CC2)C(C)(C)[C@@]12C
14	Camphene	[C@@H]12C(C)(C)C(C)[C@@H](C1)CC2
15	Camphor	C[C@@]12C(O)C[C@@H](CC1)C2(C)C
16	Carvacrol	OC1C(C)CCC(C1)C(C)C
17	Caryophyllene oxide	C[C@@]12[C@H](O1)CCC(C)[C@@H]3[C@H](C(C3)(C)C)CC2
18	Catechin	OC1CC(O)CC(C12)O[C@@H]([C@@H](O)C2)C3CC(O)C(O)CC3
19	Citral alpha	OCCC(C)CCCC(C)C
20	Columbamine	C1CC(OC)C(OC)C(C2)C1CC(N23)C4C(CC3)CC(OC)C(O)C4
21	D-limonene	CC(C)[C@@H]1CCC(C)CC1
22	Daucosterol	O[C@@H]1[C@@H](O)[C@H](O)[C@@H](CO)O[C@H]1O[C@@H](CC2)CC(=CC3)[C@@]2(C)[C@@H](CC4)[C@@H]3[C@@H]([C@]45C)CC[C@@H]5[C@H](C)CC[C@H](C(C)C)CC
23	Eelemicin	COC(C1)C(OC)C(OC)CC1CCC
24	Eicosamethyl-cyclodecasiloxane	C[Si]1(C)O[Si](C)(C)O[Si](C)(C)O[Si](C)(C)O[Si](C)(C)O[Si](C)(C)O[Si](C)(C)O[Si](C)(C)O[Si](O1)(C)C

25	Estragole	C1CC(OC)CCC1CCC
26	Glucomoringin	O[C@H]1[C@H](O)[C@@H](CO)O[C@H]([C@@H]1O)SC(NOS(=O)(=O)O)CCC(CC2)CCC2O[C@@H]([C@@H]3O)O[C@H](C)[C@@H](O)[C@@H]3O
27	Lupeol	C1C[C@H](O)C(C)(C)[C@H](CC2)[C@@]1(C)[C@H]3CC[C@@H]([C@]4(C)[C@]23C)[C@@H]5[C@@](C)(CC4)CC[C@H]5C(C)=C
28	Lutein	C1[C@H](O)CC(C)=C(C1(C)C)/C=C/C(C)=C/C=C/C(C)=C/C=C/C=C(\C)/C=C/C=C(\C)/C=C/[C@H](C2(C)C)C(C)=C[C@@H](C2)O
29	Lycopene	CC(C)=CCC/C(C)=C/C=C/C(C)=C/C=C/C(C)=C/C=C/C=C(\C)/C=C/C=C(\C)/C=C/C=C(\C)CCC=C(C)C
30	Mesitol	CC1C(O)C(C)CC(C1)C
31	N-valeramide	OC(N)CCCC
32	Niazinin	COC(S)NCC(CC1)CCC1O[C@@H]([C@@H]2O)O[C@@H](C)[C@H](O)[C@H]2O
33	Oleanolic acid	C1C[C@H](O)C(C)(C)[C@H](CC2)[C@@]1(C)[C@H]([C@@]23C)CC=C4[C@@]3(C)CC[C@]5(C(=O)O)[C@H]4CC(C)(C)CC5
34	Olenolic acid	C1C[C@H](O)C(C)(C)[C@@H]([C@]12C)CC[C@]3(C)[C@@H]2CC=C4[C@@]3(C)CC[C@]5(C(=O)O)[C@H]4CC(C)(C)CC5
35	Physicon	C1C(C)CC(O)C(C12)C(O)C3C(C2O)CC(OC)CC3O
36	Piceatannol	C1CC(O)C(O)CC1CCC2CC(O)CC(O)C2
37	Pterygospermin	C1CCCCC1CN2C(S)O[C@@]2(CC3)CC[C@]34OC(S)N4CC5CCCCC5
38	Rubiadin	OC1C(C)C(O)CC(C12)C(O)C3C(C2O)CCCC3
39	Syringol	COC1C(O)C(OC)CCC1
40	Thalidasine	CN1CCc(c2[C@@H]13)cc(OC)c(OC)c2Oc4c5c(cc(OC)c4OC)[C@@H](N(C)CC5)Cc6ccc(cc6)Oc7cc(C3)ccc7OC

41	Thalisopine	CN1CCc(c2[C@@H]13)c(O)c(OC)c(OC)c2Oc4cc5c(cc4OC)CCN(C)[C@H]5Cc6cc(c(OC)cc6)Oc7ccc(C3)cc7
42	Thalrugosaminine	CN1CCc(c2[C@@H]13)c(OC)c(OC)c(OC)c2Oc4cc5c(cc4OC)CCN(C)[C@H]5Cc6cc(c(OC)cc6)Oc7ccc(C3)cc7
43	Thalrugosidine	CN1CCc(c2[C@@H]13)cc(OC)c(O)c2Oc4c5c(cc(OC)c4OC)[C@@H](N(C)CC5)Cc6ccc(cc6)Oc7cc(C3)ccc7OC
44	Trimyristin	CCCCCCCCCCCCCC(=O)OCC(OC(=O)CCCCCCCCCCCCC)COC(=O)CCCCCCCCCCCCC
45	Ursolic acid	C1C[C@@H](C)[C@H](C)[C@H]([C@]12C(=O)O)C=3[C@@](C)(CC2)[C@@]4(C)[C@H](CC3)[C@]5(C)[C@@H](CC4)C(C)(C)[C@@H](O)CC5
46	Vinylguaiacol	C1CCC(OC)C(O)C1CC
47	Vinyllithium	[CH-]=C.[Li+]
48	Zeaxanthin	C1[C@H](O)CC(C)=C(C1(C)C)/C=C/C(C)=C/C=C/C(C)=C/C=C/C=C(C)/C=C/C=C(C)/C=C/C(C2(C)C)=C(C)C[C@H](C2)O
49	p-Tolualdehyde	OCC(CC1)CCC1C

Table S2: Phytochemicals showing lower docking scores than the control.

Entry no.	**Title**	**Smiles**	**Docking score (kcal/mol)**	**MMGBSA dG° (kcal/mol)**
1	Epigallocatechin Gallate	Oc1cc(O)cc(c12)O[C@H](c3cc(O)c(O)c(O)c3)[C@@H](C2)OC(=O)c4cc(O)c(O)c(O)c4	-9.693	-48.09
2	Theaflavin 3-gallate	Oc(c1)c(O)c(O)cc1C(=O)O[C@@H](C2)[C@@H](Oc(c23)cc(O)cc3O)c4cc(O)c(O)c(c45)c(=[OH+])c(O)cc(c5)[C@H]([C@H](O)C6)Oc(c67)cc(O)cc7O	-9.687	-66.85
3	Matairesinol	c1cc(O)c(OC)cc1C[C@@H](C(=O)OC2)[C@H]2Cc3cc(OC)c(O)cc3	-9.631	-38.48

4	Rutin	O[C@@H]1[C@@H](O)[C@H](C)O[C@H]([C@@H]1O)OC[C@H]2O[C@H]([C@H](O)[C@@H](O)[C@@H]2O)Oc(c3=O)c(-c4cc(O)c(O)cc4)oc(c35)cc([O-])cc5O	-9.607	-12.83
5	Chryophanol	C1[C@@H](C)C[C@@H](O)[C@@H]([C@H]12)[C@H](O)[C@H]3[C@H]([C@@H]2O)CCC[C@@H]3O	-9.508	-26.3
6	Vitexin	O[C@@H]1[C@@H](O)[C@H](O)[C@@H](CO)O[C@H]1c2c(O)cc(O)c(c23)c(=O)cc(o3)-c4ccc(O)cc4	-9.484	-54.44
7	Isovitexin	O[C@@H]1[C@@H](O)[C@H](O)[C@@H](CO)O[C@H]1c(c2O)c(O)cc(c23)oc(cc3=O)-c4ccc(O)cc4	-9.375	-51.15
8	Fisetin	c1cc(O)cc(c12)oc(c(O)c2=O)-c3cc(O)c(O)cc3	-9.325	-56.02
9	Eriodictyol-7-glucuronide	O[C@@H]1[C@@H](C([O-])=O)O[C@H]([C@H](O)[C@H]1O)Oc(c2)cc(O)c(c23)C(=O)C[C@@H](O3)c4cc(O)c(O)cc4	-9.198	-40.15
10	Gallocatechin gallate	Oc1cc(O)cc(c12)O[C@H](c3cc(O)c(O)c(O)c3)[C@H](C2)OC(=O)c4cc(O)c(O)c([O-])c4	-9.1	-13.39
11	Morin	Oc1cc(O)cc(c12)oc(c(O)c2=O)-c3c(O)cc(O)cc3	-9.042	-42.26
12	Betanin	OC[C@H]1O[C@H]([C@H](O)[C@@H](O)[C@@H]1O)Oc(c2)c(O)cc(c23)N([C@@H](C3)C([O-])=O)/C=C/C4=CC(C([O-])=O)=[NH+][C@@H](C4)C([O-])=O	-9.028	-24.49
13	Catechin gallate	Oc1cc(O)cc(c12)O[C@@H](c3cc(O)c(O)cc3)[C@@H](C2)OC(=O)c4cc(O)c([O-])c(O)c4	-9.014	-41.95
14	Quinizarin	O[C@@H]1CC[C@@H](O)[C@@H]([C@H]12)[C@H](O)[C@@H]3[C@@H]([C@@H]2O)CCCC3	-8.999	-34.61
15	Ellagic Acid	O=c1oc2c(O)c([O-])cc3c(=O)oc4c(O)c(O)cc1c4c23	-8.982	-41.43
16	Isoliquiritigenin	c1cc([O-])cc(O)c1C(=O)\C=C\c2ccc(O)cc2	-8.955	-9.24

17	Noroxyhydrastinine	O1COc(c2)c1cc(c23)C(=O)NCC3	-8.765	-35.48
18	Naringenin	Oc1cc(O)cc(c12)O[C@@H](CC2=O)c3ccc(O)cc3	-8.763	-42.59
19	Rohitukine	C[N@@H+]1C[C@@H](O)[C@H](CC1)c2c(O)cc(O)c(c23)c(=O)cc(o3)C	-8.704	-28.33
20	Silibinin	c1cc(O)c(OC)cc1[C@@H](O2)[C@@H](CO)Oc(c23)ccc(c3)[C@H]([C@@H](O)C4=O)Oc(c45)cc(O)cc5O	-8.686	-56.75
21	Taxifolin	Oc1cc([O-])cc(c12)O[C@@H]([C@@H](O)C2=O)c3cc(O)c(O)cc3	-8.655	-19.42
22	Butein	c1cc(O)cc(O)c1C(=O)\C=C\c2cc(O)c(O)cc2	-8.469	-49.24
23	Theaflavin-3,3-digallate	c1c(O)c(O)c(O)cc1C(=O)O[C@H](Cc(c23)c(O)cc(c3)O)[C@H](O2)c(c4)cc(O)c(=[OH+])c(c45)c(O)c(O)cc5[C@H](Oc(c67)cc(O)cc7O)[C@H](C6)OC(=O)c8cc(O)c(O)c(c8)O	-8.458	-36.56
24	Curcumin	c1cc(O)c(OC)cc1/C=C/C(=O)CC(=O)\C=C\c2cc(OC)c(O)cc2	-8.43	-41.88
25	Baicalein	Oc1c(O)c(O)cc(c12)oc(cc2=O)-c3ccccc3	-8.425	-51.72
26	Apigenin	Oc1cc([O-])cc(c12)oc(cc2=O)-c3ccc(O)cc3	-8.294	-12.59
27	Nordihydroguaiaretic acid	c1cc(O)c(O)cc1C[C@@H](C)[C@H](C)Cc2cc(O)c(O)cc2	-8.221	-35.73
28	Enterodiol	c1ccc(O)cc1C[C@@H](CO)[C@H](CO)Cc2cc(O)ccc2	-8.183	-35.09
29	Theveside	[O-]C(=O)C1=CO[C@H]([C@@H]([C@@]12O)C(=CC2)CO)O[C@@H]3O[C@H](CO)[C@@H](O)[C@H](O)[C@H]3O	-8.117	-30.2
30	Galangin	Oc1cc(O)cc(c12)oc(c(O)c2=O)-c3ccccc3	-7.959	-40.63
31	Epigallocatechin	Oc1cc(O)cc(c12)O[C@@H]([C@H](O)C2)c3cc(O)c(O)c(O)c3	-7.904	-45.82

32	Chrysin	Oc1cc([O-])cc(c12)oc(cc2=O)-c3ccccc3	-7.84	-8.1
33	Caffeic acid phenethyl ester	c1ccccc1CCOC(=O)\C=C\c2cc(O)c(O)cc2	-7.838	-57
34	Alpha-D-Glucose	OC[C@H]1O[C@H](O)[C@H](O)[C@@H](O)[C@@H]1O	-7.823	-27.7
35	Ferulic acid	c1cc(O)c(OC)cc1/C=C/C([O-])=O	-7.79	-15.83
36	O-Desmethylangolensin	c1cc(O)cc(O)c1C(=O)[C@@H](C)c2ccc(O)cc2	-7.749	-27.23
37	Enterolactone	c1ccc(O)cc1C[C@@H](C(=O)OC2)[C@H]2Cc3cc(O)ccc3	-7.747	-41.33
38	Meso-dihydroguaiaretic acid	c1cc(O)c(OC)cc1C[C@H](C)[C@H](C)Cc2cc(OC)c(O)cc2	-7.726	-23.56
39	Gallic acid	O[C@@H](C1)[C@@H](O)[C@@H](O)C[C@@H]1C(O)O	-7.53	-33.03
40	Alizarin	O[C@@H]1[C@@H](O)CC[C@@H]([C@H]12)[C@@H](O)[C@H]3[C@H]([C@@H]2O)CCCC3	-7.333	-36.31
41	5'-Hydroxy-O-desmethylangolensin	Oc(c1)c(O)cc(O)c1C(=O)[C@H](C)c2ccc(O)cc2	-7.332	-42.39
42	Lariciresinol	c1cc(O)c(OC)cc1[C@H]2OC[C@@H]([C@@H]2CO)Cc3cc(OC)c(O)cc3	-7.265	-49.92
43	Genistein	Oc1cc(O)cc(c12)occ(c2=O)-c3ccc(O)cc3	-7.264	-40.49
44	3'-Hydroxy-O-desmethylangolensin	c1cc(O)c(O)c(O)c1C(=O)[C@@H](C)c2ccc(O)cc2	-7.255	-44.11
45	Tambulin	Oc1cc(OC)c(OC)c(c12)oc(c(O)c2=O)-c3ccc(OC)cc3	-7.232	-56.78
46	Plumbagin	c1ccc(O)c(c12)C(=O)C=C(C2=O)C	-7.149	-36.71
47	Thalirugidine	COc(c1)c(OC)c(O)c(c12)CC[N@H+](C)[C@H]2Cc3cc(c(OC)cc3)Oc(cc4)ccc4C[C@@H]5[N@H+](C)CCc(c56)c(O)c(OC)c(c6)OC	-7.124	-54.21
48	Resveratrol	Oc(c1)cc(O)cc1/C=C/c2ccc(O)cc2	-7.123	-45.61
49	Eugenol	C=CCc1cc(OC)c(O)cc1	-7.095	-36.33

50	Indole-3-carbinol	OCc1c[nH]c(c12)cccc2	-7.014	-29.31
51	2'-Hydroxychalcone	c1cccc(O)c1C(=O)\C=C\c2ccccc2	-6.999	-36.64
52	Hesperetin	Oc1cc(O)cc(c12)O[C@@H](CC2=O)c3cc(O)c(OC)cc3	-6.956	-38.04
53	6-O-Methylequol	COc(c1)c(O)cc(c12)OC[C@@H](C2)c3ccc(O)cc3	-6.954	-41.17
54	3'-O-Methylequol	c1cc(O)cc(c12)OC[C@@H](C2)c3cc(OC)c(O)cc3	-6.835	-35.59
55	Coumestrol	Oc(c1)ccc2c1oc(c23)c4c(oc3=O)cc(O)cc4	-6.798	-43.18
56	4-Hydroxycinnamic acid	c1cc(O)ccc1/C=C/C([O-])=O	-6.797	-13.36
57	Biochanin A	Oc1cc(O)cc(c12)occ(c2=O)-c3ccc(OC)cc3	-6.78	-43.97
58	Flavone	c1cccc(c12)oc(cc2=O)-c3ccccc3	-6.768	-40.23
59	Daidzein	c1cc(O)cc(c12)occ(c2=O)-c3ccc(O)cc3	-6.697	-41.02
60	6'-Hydroxy-O-desmethylangolensin	c1cc(O)ccc1[C@H](C)C(=O)c2c(O)cc(O)cc2O	-6.681	-36.89
61	N-(4-hydroxyundecanoyl) anabasine	c1ncccc1[C@H](CCCC2)N2C(=O)CC[C@@H](O)CCCCCCC	-6.668	-42.37
62	Isoxanthohumol	c1cc(O)ccc1[C@@H](O2)CC(=O)c(c23)c(OC)cc(O)c3CC=C(C)C	-6.663	-43.48
63	Juglone	O[C@H]1CCC[C@@H]([C@H]12)[C@@H](O)CC[C@H]2O	-6.629	-21.75
64	Methoxyeugenol	COc(c1)c(O)c(OC)cc1CC=C	-6.627	-36.44
65	7,4'-Dihydroxyflavone	Oc1ccc(cc1)-c(cc2=O)oc(c23)cc(O)cc3	-6.58	-44.69
66	Equol	c1cc(O)cc(c12)OC[C@@H](C2)c3ccc(O)cc3	-6.519	-40.76
67	Thalirugine	COc(c1)c(OC)c(O)c(c12)CC[N@@H+](C)[C@H]2Cc3ccc(cc3)Oc(c(OC)cc4)cc4C[C@@H]5[N@@H+](C)CCc(c56)cc(OC)c(O)c6	-6.484	-42.92
68	Germacranolide	C[C@@H]1C(=O)O[C@@H]([C@H]12)/C=C(C)\CC[C@H](O)/C(C)=C\[C@@H]2O	-6.429	-23.42
69	Safrole	O1COc(c12)ccc(c2)CC=C	-6.417	-34.01

70	Thymol	CC(C)c1c(O)cc(C)cc1	-6.412	-33.18
71	6-hydroxy-3-(4-methoxyphenyl)-4-methylcoumarin	c1cc(O)cc(c12)c(C)c(c(=O)o2)-c3ccc(cc3)OC	-6.379	-46.31
72	Aloe-emodin	OC[C@H](C1)C[C@@H](O)[C@@H]([C@H]12)[C@@H](O)[C@H]3[C@H]([C@@H]2O)CCC[C@@H]3O	-6.364	-35.92
73	Anthrone	C1CCC[C@H]([C@@H]12)[C@H](O)[C@@H]3[C@@H](C2)CCCC3	-6.36	-28.96
74	Anthraquinone	C1CCC[C@@H]([C@@H]2O)[C@@H]1[C@H](O)[C@H]([C@@H]23)CCCC3	-6.332	-30.27
75	Myristicin	O1COc(c12)cc(CC=C)cc2OC	-6.31	-37.85
76	Pterostilbene	COc(c1)cc(OC)cc1/C=C/c2ccc(O)cc2	-6.143	-27.26
77	Piperolein A	C1CCCCN1C(=O)CCCC/C=C/c(c2)ccc(c23)OCO3	-6.13	-38.4
78	4-hydroxychalcone	c1cc(O)ccc1/C=C/C(=O)c2ccccc2	-6.108	-41
79	Thymoquinone	O=C1C=C(C)C(=O)C=C1C(C)C	-6.092	-30.27
80	Capsaicin	CC(C)/C=C/CCCCC(=O)NCc1cc(OC)c(O)cc1	-6.075	-35.19
81	Piperolein B	C1CCCCN1C(=O)CCCCCC/C=C/c(c2)ccc(c23)OCO3	-6.058	-33.5
82	Phytic acid	[O-]P(=O)(O)O[C@H]1[C@H](OP([O-])([O-])=O)[C@H](OP([O-])(=O)O)[C@H](OP(=O)(O)O)[C@@H](OP([O-])(=O)O)[C@H]1OP([O-])(=O)O	-6.003	16.22
83	Xanthohumol	CC(C)=CCc1c(O)c(c(OC)cc1O)C(=O)/C=C/c2ccc(O)cc2	-5.902	-43.49
84	Nimbiol	c1c(C)c(O)cc2c1C(=O)C[C@H]([C@@]23C)C(C)(C)CCC3	-5.861	-28.31
85	Acacetin	Oc1cc(O)cc(c12)oc(cc2=O)-c3ccc(OC)cc3	-5.855	-39.35

86	Benzeneethanamine	[NH3+]CCC1CCCCC1	-5.833	-16.46
87	Alliin	CCC[S+](O)C[C@H]([NH3+])C(O)O	-5.73	-42.4
88	Caffeic Acid	c1cc(O)c(O)cc1/C=C/C([O-])=O	-5.704	-20.24
89	Glabridin	C1=CC(C)(C)Oc(cc2)c1c(c23)OC[C@H](C3)c4c(O)cc(O)cc4	-5.661	-31.09
90	Alpha-Mangostin	CC(C)=CCc(c(O)c1)c(O)c(c2=O)c1oc(c23)cc(O)c(OC)c3CC=C(C)C	-5.656	-43.34
91	Dantron	C1CC[C@@H](O)[C@H]([C@H]2O)[C@@H]1[C@H](O)[C@H]([C@H]23)CCC[C@@H]3O	-5.589	-0.46
92	Jatrorrhizine	c1cc(OC)c(OC)c(c2)c1cc([n+]23)c4c(CC3)cc(O)c(c4)OC	-5.569	-66.61
93	Pinoresinol	c1cc(O)c(OC)cc1[C@H]2OC[C@@H]([C@@H]23)[C@H](OC3)c4cc(OC)c(O)cc4	-5.53	-23.83
94	Flavanone	c1cccc(c12)O[C@@H](CC2=O)c3ccccc3	-5.454	-32.31
95	Theaflavin	Oc1cc(O)cc(c12)O[C@@H]([C@H](O)C2)c3cc(O)c(O)c(c34)c(=[OH+])c(O)cc(c4)[C@H]([C@H](O)C5)Oc(c56)cc(O)cc6O	-5.409	-39.39
96	3,3'-Diindolylmethane	c1cccc(c12)[nH]cc2Cc3c[nH]c(c34)cccc4	-5.375	-28.3
97	Guaiol	OC(C)(C)[C@@H](C1)CC[C@H](C)C(=C12)CC[C@@H]2C	-5.347	-13.84
98	7,8-benzoflavone	c1ccccc1-c(o2)cc(=O)c3ccc(c4c23)cccc4	-5.334	-36.05
99	Piperine	C1CCCCN1C(=O)/C=C/C=C/c(c2)ccc(c23)OCO3	-5.282	-42.29
100	4-benzyl-7-methoxy-3-phenylcoumarin	c1cc(OC)cc(c12)oc(=O)c(-c3ccccc3)c2Cc4ccccc4	-5.271	-29.68
101	4-Benzyl-3(4'-chlorophenyl)-7-hydroxycoumarin	Oc1cc(O)cc(c12)oc(c(O)c2=O)-c3cc(O)c(O)cc3	-5.267	-31.49
102	Clicoemodin	O[C@H]1[C@@H](O)[C@@H](CO)O[C@@H]([C@@H]1O)O[C@H](C2)C[C@@H](O)[C@@H]([C@H]23)[C@@H](O)[C@H]4[C@H]([C@H]3O)C[C@H](C)C[C@@H]4O	-5.244	-25.76
103	Geranyl acetate	O=C(C)OC\C=C(C)\CCC=C(C)C	-5.237	-31.91

104	Protocatechuic acid	c1cc(O)c(O)cc1C([O-])=O	-5.154	-15.02
105	Centratherin	O=C1C=C(O[C@@]12C)/C(CO)=C\[C@@H]3[C@H](C(C(O3)=O)=C)[C@H](C2)OC(=O)/C(C)=C\C	-5.086	-8.29
106	Isoamaranthin	O[C@@H]1[C@@H](O)[C@H](O)[C@@H](C([O-])=O)O[C@H]1O[C@@H]2[C@@H](O)[C@H](O)[C@@H](CO)O[C@H]2Oc(c3)c(O)cc(c34)[N+](\[C@H](C4)C([O-])=O)=C\CC5=CC(C([O-])=O)=[NH+][C@@H](C5)C([O-])=O	-5.057	-32.52
107	Cucubitacin B	CC(=O)OC(C)(C)/C=C/C(=O)[C@](C)(O)[C@@H]([C@@H](C1)O)[C@](C)([C@@]12C)CC(=O)[C@]3(C)[C@H]2CC=C4[C@H]3C[C@H](O)C(=O)C4(C)C	-5.014	-38.32
108	Piperlongumine	COc(c1)c(OC)c(OC)cc1\C=C\C(=O)N2CCC=CC2=O	-5.014	-18.48
109	Gingerol	CCCCC[C@H](O)CC(=O)CCc1cc(OC)c(O)cc1	-4.999	-36.69
110	anthocyanin	c1cccc(c12)[o+]c(cc2)-c3ccccc3	-4.983	-50.62
111	3-(4-bromophenyl)-7-hydroxy-4-phenylcoumarin	c1ccccc1-c(c(c23)ccc(c3)O)c(c(=O)o2)-c4ccc(Br)cc4	-4.871	-35.96
112	Hypericin	c12c3c4c5c6c1c(c(=O)cc6C)c(O)c7c2c(c(O)cc7O)c8c3c(c(O)cc8O)c(O)c4c(=O)cc5C	-4.867	-23.43
113	4-O-Methyl equol	c1cc(O)cc(c12)OC[C@@H](C2)c3ccc(OC)cc3	-4.857	-35.46
114	Lambertine	O1COc(c2)c1cc(CC3)c2C(N34)=Cc5c(C4)c(OC)c(OC)cc5	-4.837	-31.8
115	Oxymatrine	[O-][N@@+]12[C@@H]3[C@H](CCC1)[C@@H]4N(C(=O)CCC4)C[C@@H]3CCC2	-4.759	-10.8

116	1'-Acetoxychavicol acetate	O=C(C)O[C@@H](C=C)c1ccc(cc1)OC(=O)C	-4.69	-25.75
117	Delta_cadinene	CC(=C1)CCC([C@@H]12)=C(C)CC[C@H]2C(C)C	-4.678	-17.39
118	Sulfrophane	C[S@](=O)CCCCN=C=S	-4.674	-32.81
119	5,6-benzoflavone	c1ccccc1-c(cc2=O)oc3ccc(c4c23)cccc4	-4.652	-38.41
120	Parthenolide	C[C@@]12[C@H](O1)[C@@H]3[C@H](C(C(O3)=O)=C)CC/C(C)=C\CC2	-4.621	-20.23
121	Benzyl isothiocyanate	S=C=NCc1ccccc1	-4.62	-30.74
122	Carveol	C1C=C(C)[C@H](O)C[C@@H]1C(C)=C	-4.62	-28.48
123	Cinnamic acid	[O-]C(=O)\C=C\c1ccccc1	-4.588	-6.88
124	Beta-Sitosterol-beta-D-Glucoside	O[C@H]1[C@H](O)[C@@H](CO)O[C@H]([C@@H]1O)O[C@H](CC2)CC(=CC3)[C@@]2(C)[C@@H](CC4)[C@@H]3[C@@H]([C@]45C)CC[C@@H]5[C@H](C)CC[C@H](C(C)C)CC	-4.555	-38.15
125	Isoelemicin	COc(c1)c(OC)c(OC)cc1/C=C/C	-4.399	-26.55
126	Acetic acid	OC(O)C	-4.359	-15.81
127	Nobiletin	COc1c(OC)c(OC)c(OC)c(c12)oc(cc2=O)-c3cc(OC)c(OC)cc3	-4.354	-40.05
128	Anthrarufin	O[C@@H]1CCC[C@@H]([C@@H]2O)[C@H]1[C@@H](O)[C@@H]([C@@H]23)CCC[C@H]3O	-4.352	8.57
129	1,2-Didehydropinidinol	O[C@H](C)C[C@@H]1[NH+]=C(C)CCC1	-4.345	-43.15
130	Shogaol	c1cc(O)c(OC)cc1CCC(=O)\C=C\CCCCC	-4.283	-33.8
131	Xanthyletin	O1C(C)(C)C=Cc(c12)cc3c(c2)oc(=O)cc3	-4.265	-27.54
132	Palmatine	COc(c1)c(OC)cc(CC2)c1c([n+]23)cc4c(c3)c(OC)c(OC)cc4	-4.214	-65.22
133	Spathulenol	C1C[C@@](O)(C)[C@@H]2[C@@H]1C(=C)CC[C@H]([C@H]23)C3(C)C	-4.209	-2.41
134	Geraniol	OC\C=C(C)\CCC=C(C)C	-4.116	-33.93

135	Sterol	C1C[C@@H](O)C[C@@H](CC2)[C@H]1[C@@H]([C@H]23)CC[C@H]4[C@H]3CCC4	-4.111	8.7
136	Nerol	OC/C=C(C)\CCC=C(C)C	-4.049	-27.15
137	Oxyberberine	O1COc(c2)c1cc(CC3)c2c(n34)cc5c(c4=O)c(OC)c(OC)cc5	-3.998	-37.57
138	Beta_Bisabolene	CC1=CC[C@H](CC1)C(=C)CCC=C(C)C	-3.984	-28.45
139	Terpinolene	CC(C)=C1CCC(C)=CC1	-3.98	-25.94
140	Carnosol	Oc1c(O)c(C(C)C)cc(c1[C@]234)[C@@H](OC4=O)C[C@H]2C(C)(C)CCC3	-3.953	-25.04
141	Thalicarpine	C[N@H+]1CCc(c2[C@@H]13)cc(OC)c(OC)c2c4c(C3)cc(c(c4)OC)Oc(cc(OC)c(c5)OC)c5C[C@@H]6[N@@H+](C)CCc(c67)cc(OC)c(c7)OC	-3.927	-40.13
142	Octadecenoic acid	OC(O)CCCCCCCCCCCCCCCCCC	-3.918	-36.65
143	Hirsutine	COC(=O)C(=C\OC)\[C@H]([C@H](C1)CC)C[C@@H]([N@@H+]12)c3c(CC2)c4c([nH]3)cccc4	-3.917	-23.81
144	Isocorydine	CN1CCc(c2[C@@H]13)cc(OC)c(OC)c2c4c(C3)ccc(OC)c4O	-3.88	-25.29
145	Perillyl alcohol	OCC(=CC1)CC[C@@H]1C(C)=C	-3.874	-22.4
146	Lemonene	CC(=C)[C@H]1CCC(C)=CC1	-3.829	-31.24
147	Limonene	CC1=CC[C@H](CC1)C(=C)C	-3.829	-31.21
148	Citronellal	OCC[C@@H](C)CCCC(C)C	-3.815	-26.19
149	Piperazine	[NH2+]1CCNCC1	-3.801	-17.44
150	Beta-Caryophyllene oxide	C[C@]12[C@H](O2)CCC(=C)[C@@H]3[C@@H](CC1)C(C3)(C)C	-3.765	6.5
151	(E)-Ajoene	CCC[S+](O)CCCSSCCC	-3.642	-48.08
152	S allylmercaptocysteine	C=CCSSC[C@@H](C(=O)[O-])[NH3+]	-3.537	-10.81

153	Palmitic acid	[O-]C(=O)CCCCCCCCCCCCCCC	-3.508	-15.65
154	Heptadecanoic acid	OC(O)CCCCCCCCCCCCCCCC	-3.478	-17.42
155	Trans-Nerolidol	C=C[C@@](O)(C)CC/C=C(C)/CCC=C(C)C	-3.459	-21.18
156	Sesamin	O1COc(c12)ccc(c2)[C@H]3OC[C@@H]([C@@H]34)[C@H](OC4)c(c5)ccc(c56)OCO6	-3.441	-32.6
157	Stearic acid	[O-]C(=O)CCCCCCCCCCCCCCCCC	-3.408	-9.1
158	Alpha_pinene	CC1(C)[C@H](C2)C(C)=CC[C@@H]12	-3.299	-3.54
159	Linalool	C=C[C@@](O)(C)CCC=C(C)C	-3.285	-24.92
160	Carnosic acid	Oc1c(O)c(C(C)C)cc(c1[C@]23C(=O)[O-])CC[C@H]2C(C)(C)CCC3	-3.261	-14.85
161	Pelargic acid	OC(O)CCCCCCCCC	-3.26	-27.22
162	Hexadecanoic acid	OC(O)CCCCCCCCCCCCCCCC	-3.111	-22.41
163	Ginkoglide B	O[C@H]1C(=O)O[C@H]([C@@]12[C@]345)O[C@]3([C@]6(O)[C@H]([C@@H]5O)OC(=O)[C@H]6C)C(=O)O[C@@H]4C[C@H]2C(C)(C)C	-3.072	-25.45
164	Stigmasterol	C1C[C@H](O)CC(=CC2)[C@@]1(C)[C@@H](CC3)[C@@H]2[C@@H]([C@]34C)CC[C@@H]4[C@H](C)/C=C/[C@H](C(C)C)CC	-3.06	47.31
165	Sanguinarine	O1COc(cc2)c1c(c[n+]3C)c2c(c34)ccc5c4cc6c(c5)OCO6	-3.045	-47.88
166	Linoleic acid	OC(O)CCCCCCCCCCCCCCCCC	-3.013	-26.88
167	Beta-Sitosterol	C1C[C@H](O)CC(=CC2)[C@@]1(C)[C@@H](CC3)[C@@H]2[C@@H]([C@]34C)CC[C@@H]4[C@H](C)CC[C@H](C(C)C)CC	-2.912	-22.77
168	Glyceollin	Oc(c1)ccc2c1O[C@H]([C@]23O)c4c(OC3)c5c(cc4)OC(C)(C)C=C5	-2.81	-14.83
169	Azelaic acid	[O-]C(=O)CCCCCCCC([O-])=O	-2.734	15.84
170	Beta_pinene	CC([C@@H]12)(C)[C@@H](C2)C(=C)CC1	-2.694	-5.71
171	Colchicine	O=C(C)N[C@H]1CCc(cc(OC)c(OC)c2OC)c2c(c13)ccc(OC)c(=O)c3	-2.687	-22.47
172	Brassicasterol	C1C[C@H](O)CC(=CC2)[C@@]1(C)[C@@H](CC3)[C@@H]2[C@@H]([C@]34C)CC[C@@H]4[C@H](C)/C=C/[C@H](C)C(C)C	-2.559	-9.48

173	Lauric acid	[O-]C(=O)CCCCCCCCCCC	-2.491	-15.9
174	Myristic acid	[O-]C(=O)CCCCCCCCCCCCC	-2.471	-6.97
175	Diallyldisulfide	C=CCSSCC=C	-2.446	-26.41
176	Vernosterol	C1C[C@H](O)C[C@@H]2CCC([C@H]3[C@@]12C)=C4[C@](C)(CC3)[C@H](C=C4)[C@H](C)CC/C(C(C)C)=C/C	-2.329	-10.18
177	Myrcene	CC(C)=CCCC(=C)C=C	-2.227	-18.96
178	Octadecane	CCCCCCCCCCCCCCCCCC	-2.028	-26.34
179	16-Hentriacontanone	CCCCCCCCCCCCCCCC(=O)CCCCCCCCCCCCCCC	-1.89	-53.82
180	Betanidin	O=C(C1)C(=O)C=C(C=12)N([C@@H](C2)C([O-])=O)/C=C/C(C3)=CC(C(O)O)=N[C@@H]3C([O-])=O	-1.844	-5.85
181	1-cyanocychexylpyrrolidin	C1CCC[NH+]1C2CCCCC2	-1.261	-34.78
182	Oxycanthine	C[N@H+]1CCc(c2[C@H]13)cc(OC)c(OC)c2Oc4cc5c(cc4OC)CC[N@H+](C)[C@@H]5Cc6cc(c([O-])cc6)Oc7ccc(C3)cc7	-0.285	-13.6
183	Campesterol	C1C[C@H](O)CC(=CC2)[C@@]1(C)[C@@H](CC3)[C@@H]2[C@@H]([C@]34C)CC[C@@H]4[C@H](C)CC[C@@H](C)C(C)C	-0.11	44.62

Table S3: Thermodynamics binding free energy calculation at every 2ns for epicatechin and control.

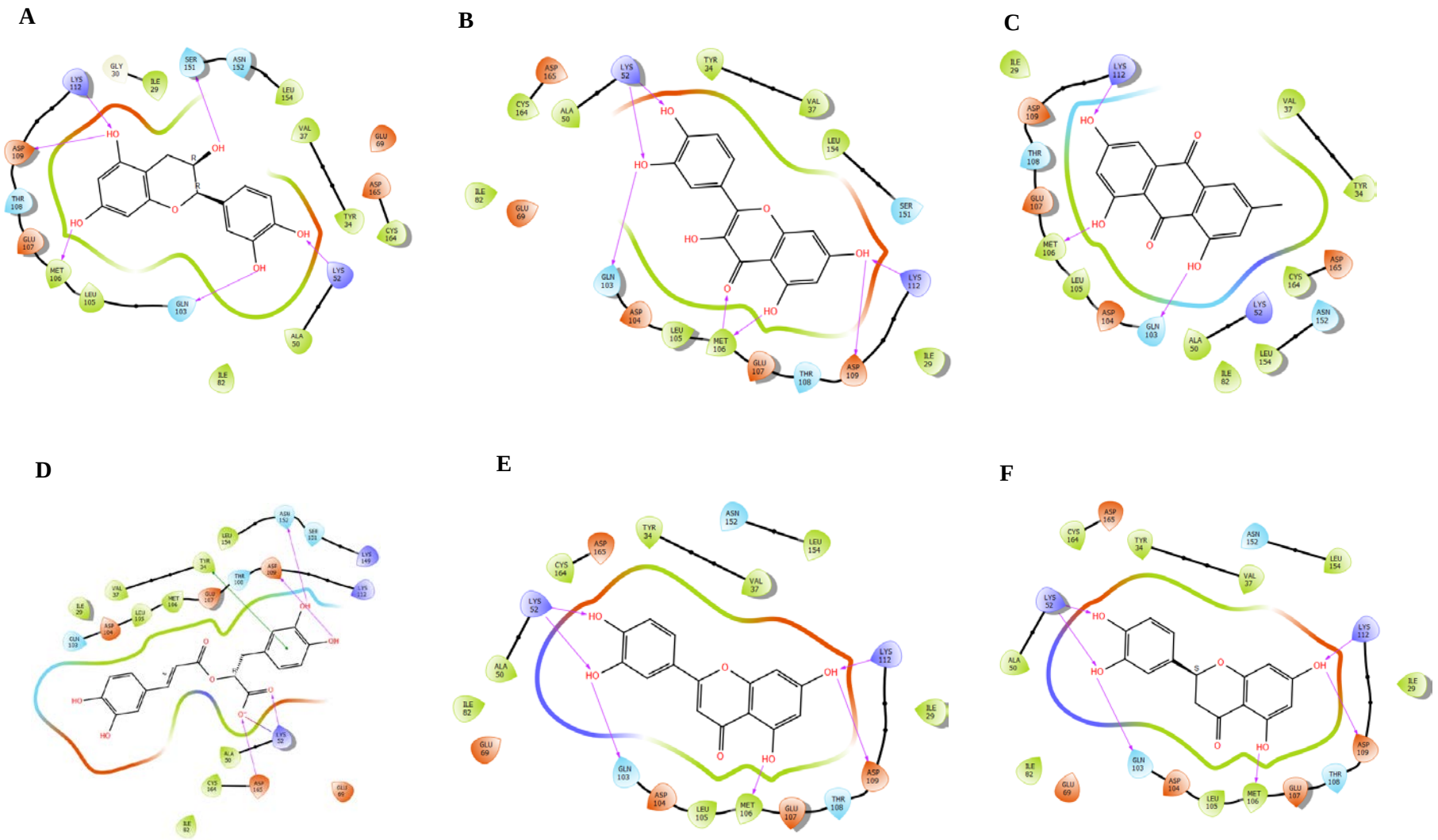
Time (ns)	Epicatechin	Control
10	-50.00	-47.29
12	-44.22	-49.25
14	-46.86	-45.11
16	-45.06	-57.19
18	-42.88	-55.21
20	-40.64	-49.26
22	-45.31	-48.76
24	-46.55	-43.77
26	-43.05	-52.11
28	-43.37	-50.72
30	-45.87	-54.50
32	-47.08	-51.39
34	-41.06	-43.22
36	-50.84	-50.19
38	-47.93	-50.03
40	-55.27	-52.68
42	-44.26	-52.62
44	-47.76	-45.89
46	-48.07	-51.19
48	-51.15	-48.83
50	-42.89	-51.35
52	-50.20	-53.61
54	-43.65	-55.97
56	-47.15	-47.74
58	-47.27	-50.29
60	-45.31	-49.64
62	-47.72	-42.66
64	-44.21	-48.06
66	-45.64	-48.41
68	-44.91	-47.52
70	-47.33	-54.30
72	-48.45	-49.69
74	-49.96	-50.20
76	-48.83	-49.40
78	-45.93	-48.52
80	-46.98	-47.54
82	-42.34	-42.02
84	-49.56	-53.69
86	-43.82	-50.92
88	-53.66	-50.94
90	-54.40	-46.49
92	-52.34	-48.35
94	-52.98	-43.40
96	-58.33	-53.61
98	-50.98	-46.99
100	-47.69	-46.92

Table S4: Occurrence of residues in favored, additional-allowed, generously allowed, and disallowed regions.

Complex	**Residues in favored region**	**Residues in the additional allowed region**	**Residues in the generously allowed region**	**Residues in the disallowed region**
Epicatechin-ERK2	265 84.9%	42 13.5%	5 1.6%	0 0.0%
Control-ERK2	259 83.0%	44 14.1%	8 2.6%	1 0.3%

Table S5: ADME profile for control and epicatechin.

Parameter	**Control**	**Epicatechin**
Molecular weight	177.13 g/mol	290.27 g/mol
No. of HBA	3	6
No. of HBD	2	5
TPSA	73.50 $A^{\circ 2}$	110.38 $A^{\circ 2}$
Log Po/w (iLOGP)	1.35	1.47
Log S (ESOL)	-2.41 (water soluble)	-2.22 (water soluble)
GI absorption	High	High
BBB permeant	No	No
CYP1A2 inhibitor	Yes	No
CYP2C19 inhibitor	No	No
CYP2C9 inhibitor	No	No
CYP2D6 inhibitor	No	No
CYP3A4 inhibitor	No	No
Lipinski	No violation	No violation


A
B
C
D
E
F

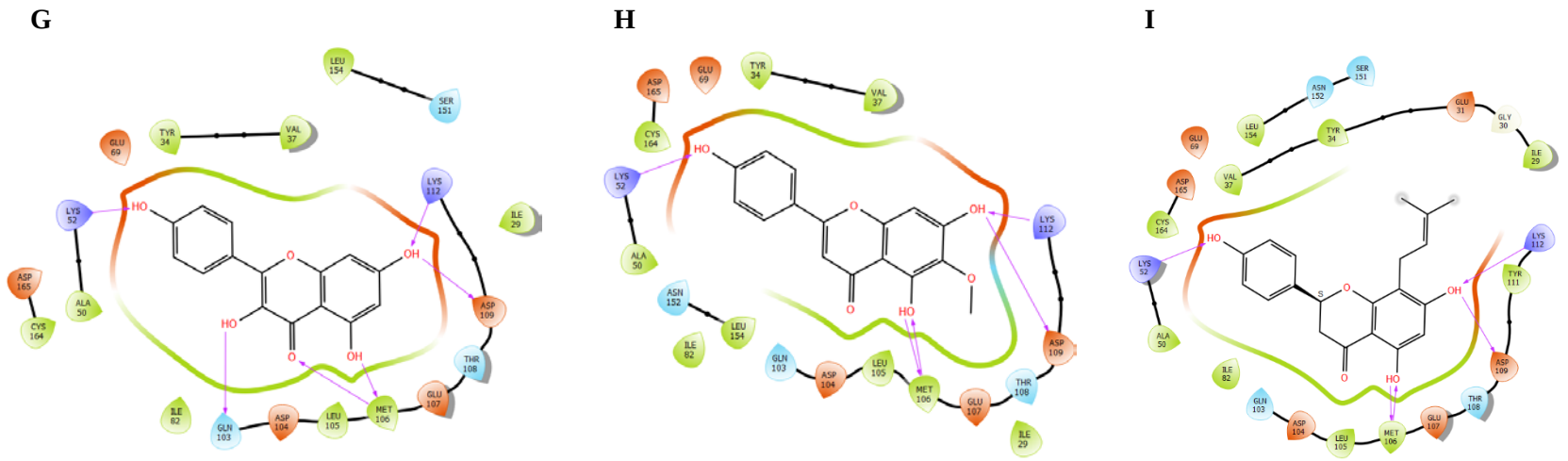


Figure S1: Protein-ligand interaction A) Epicatechin-ERK2 complex and B) Quercetin-ERK2 complex C) Emodin- ERK2 complex D) Rosmarinic acid- ERK2 complex E) Luteolin- ERK2 complex F)Eriodictyol- ERK2 complex G) Kaempferol- ERK2 complex H) Hispidulin- ERK2 complex I) 8-prenylnaringen- ERK2 complex