Supplementary information

Tissue Lipidomics, Network Pharmacology, and Molecular Docking to Explore the Therapeutic Mechanism of Anthocyanins from *Lycium ruthenicum* Murr. against Gouty Arthritis

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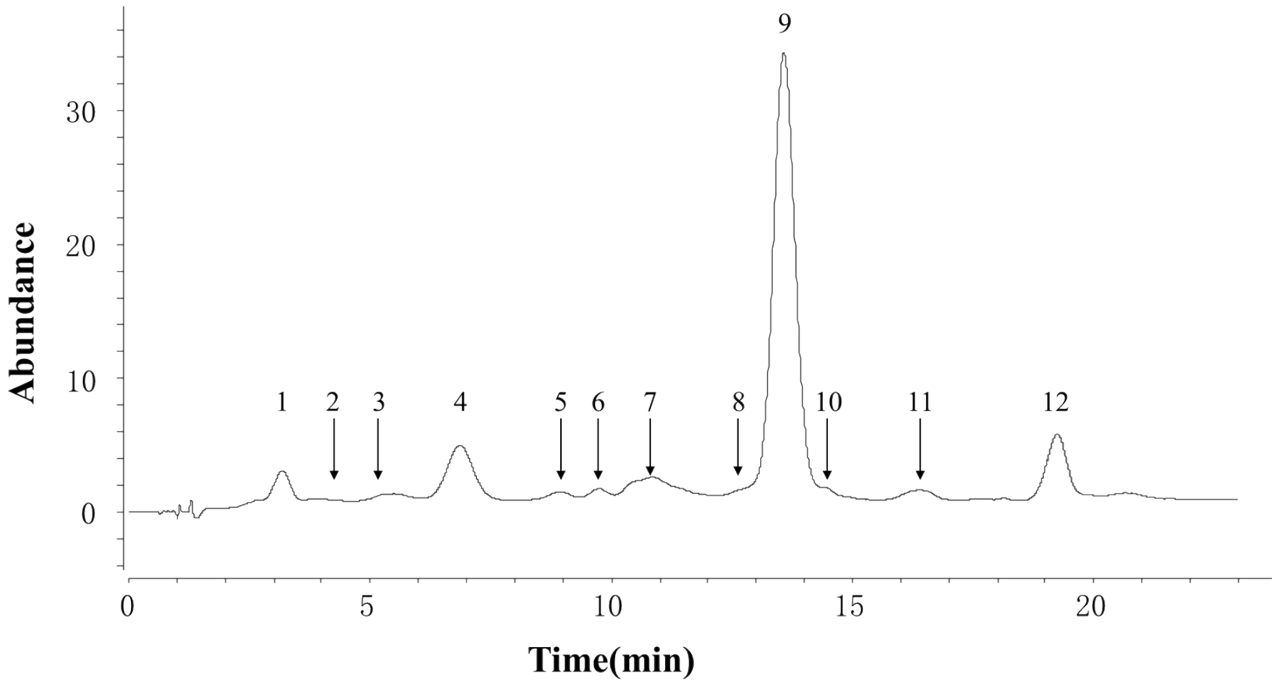


Figure S1. UPLC chromatogram at 520 nm of anthocyanins from LR. 5 mg of LR anthocyanins was dissolved in 1 mL of H_2O, filtered through a 0.2 μm membrane into a brown vial. Column: Agilent Eclipse Plus C18 (100 × 2.1 mm, 1.8 μm); Flow rate: 0.3 mL/min; Column temperature: 35℃; Solvent A: 0.1% HCOOH in H_2O, solvent B: ACN; The gradient program: 0-2 min, 5% to 10% B; 2-18 min, 10% to 17% B; 18-22 min, 17% B; 22-25 min, 17% to 35% B; 25-28 min, 35% to 5% B. The MS ionization mode was positive and the MS detection was under the following parameters: gas temperature 350°C, gas flow 10 L/min, nebulizer 30 psi, capillary voltage 3500 V, skimmer voltage 65 V, octopole RF voltage 750 V, fragmentor voltage 150 V. The full-scan MS spectra were acquired over a *m/z* range of 50-1500. The MS/MS collision energies were set at 20 and 40 eV, respectively. A reference solution was sprayed as continuous calibration using the following reference masses: *m/z* 121.0509 and 922.0098.

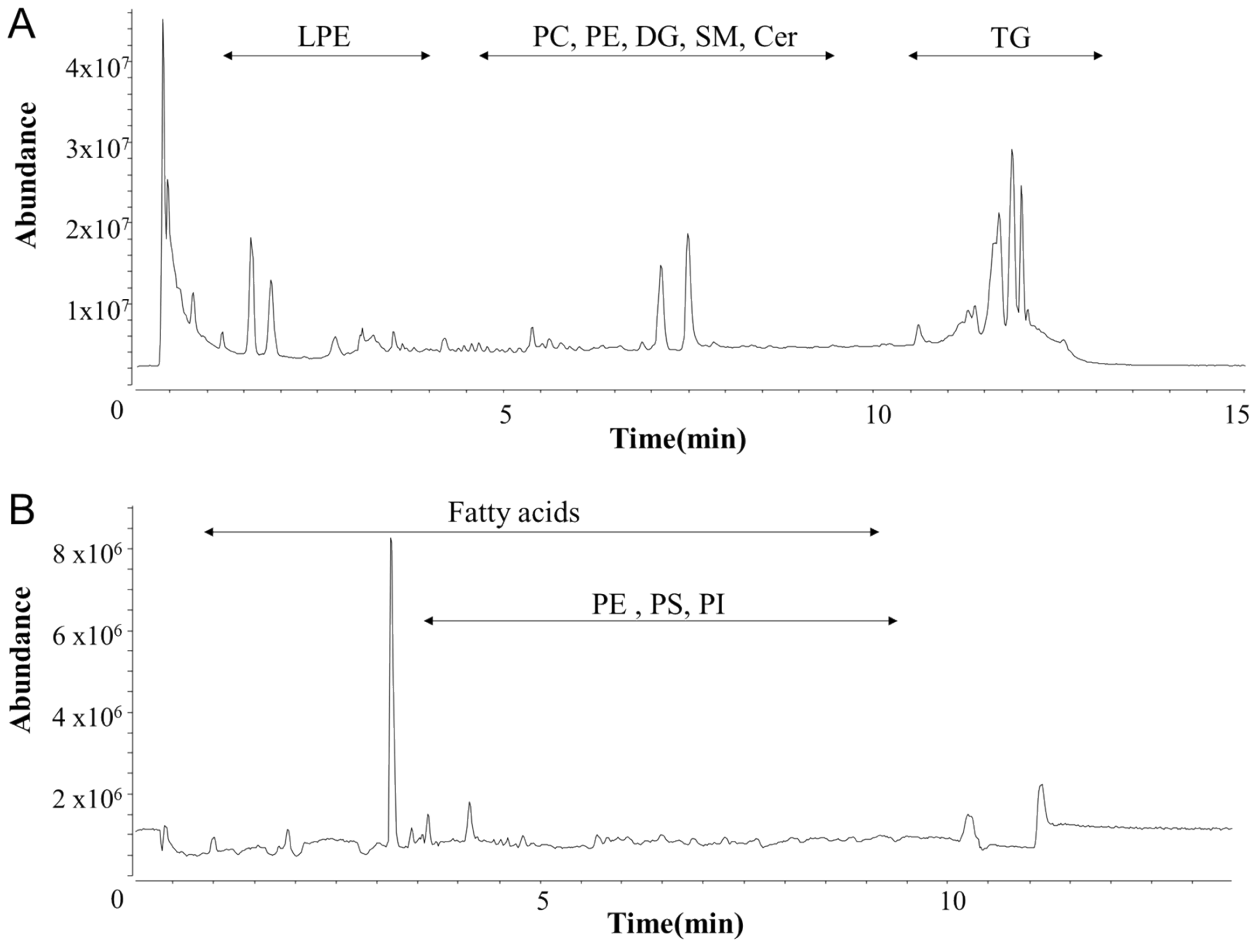
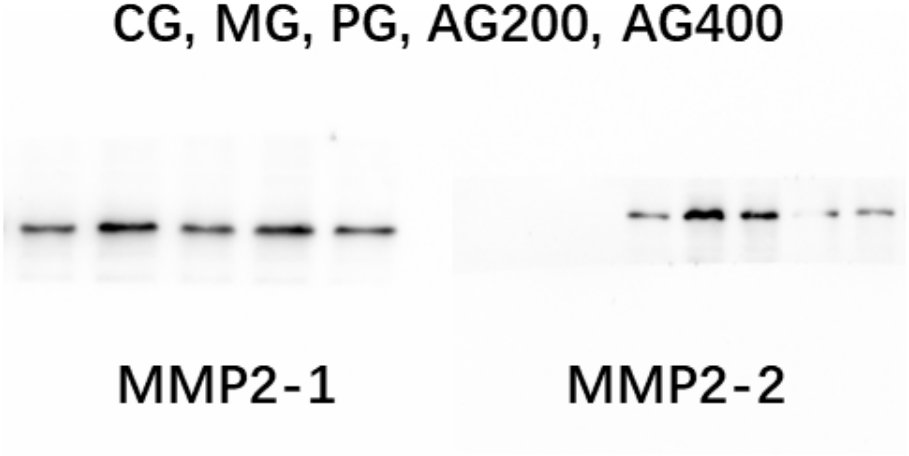


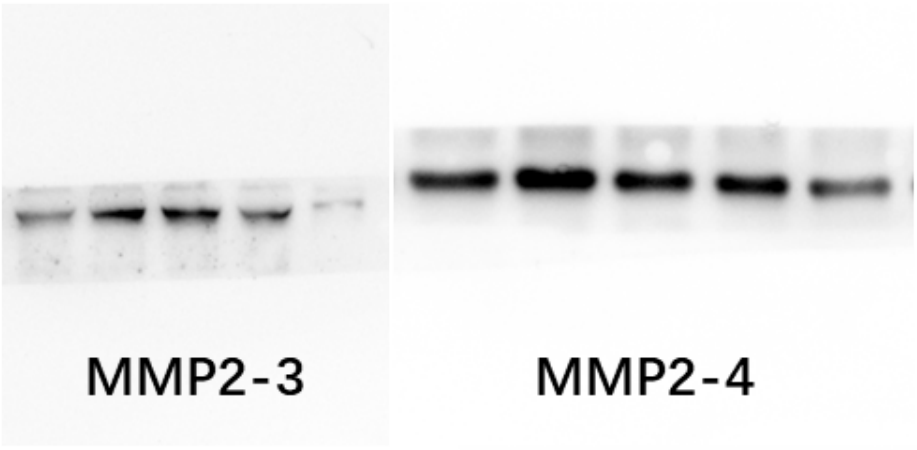
Figure S2. LC-MS TIC diagrams of mice ankle joints under (A) positive and (B) negative mode. LPE: Lysophosphatidylethanolamine, PC: Phosphatidylcholine, PE: Phosphatidylethanolamine, DG: Diacylglycerol, SM: Sphingomyelin, Cer: Ceramide, TG: Triacylglycerol, PS: Phosphatidylserine, PI: Phosphatidylinositol.

CG, MG, PG, AG200, AG400



MMP2-1 MMP2-2

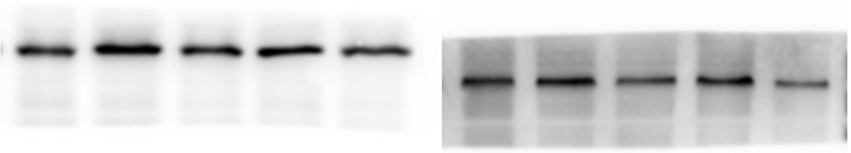
α-Tubulin-1 α-Tubulin-2



MMP2-3 MMP2-4

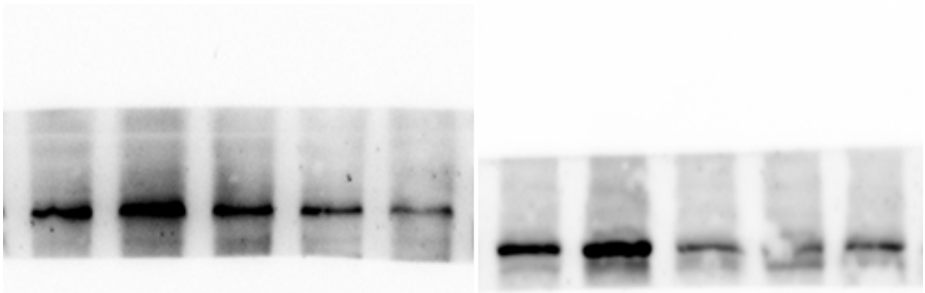
α-Tubulin-3 α-Tubulin-4

CG, MG, PG, AG200, AG400

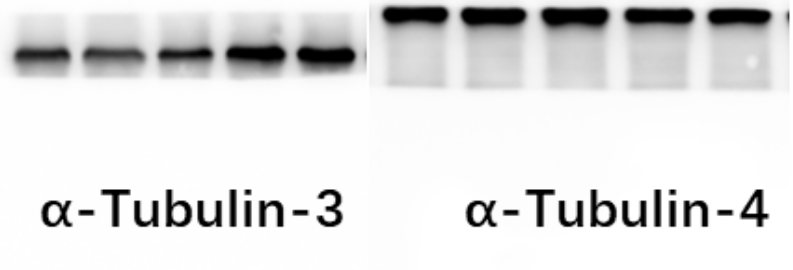


MMP9-1 MMP9-2

α-Tubulin-1 α-Tubulin-2

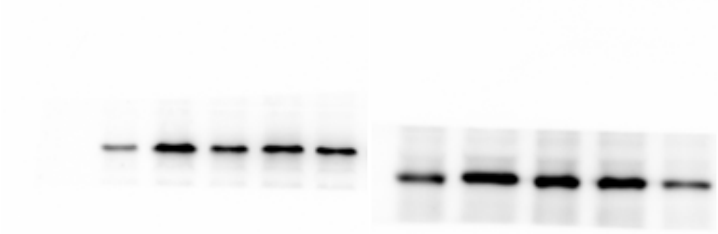


MMP9-3 MMP9-4

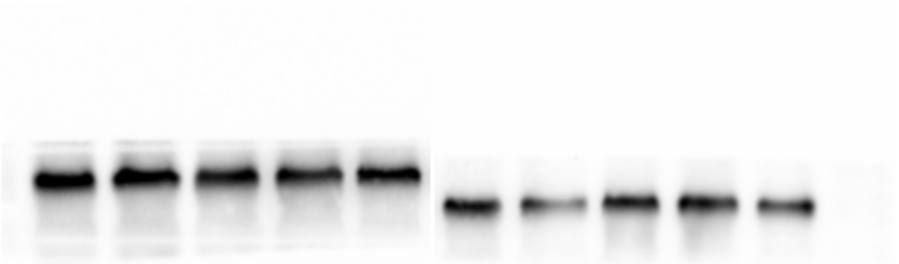


α-Tubulin-3 α-Tubulin-4

CG, MG, PG, AG200, AG400

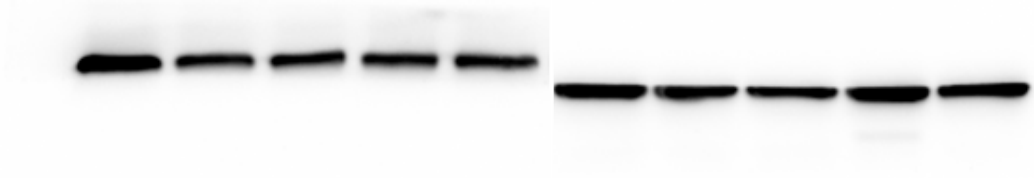


MAP2K1-1 MAP2K1-2



α-Tubulin-1 α-Tubulin-2

MAP2K1-3 MAP2K1-4



α-Tubulin-3 α-Tubulin-4

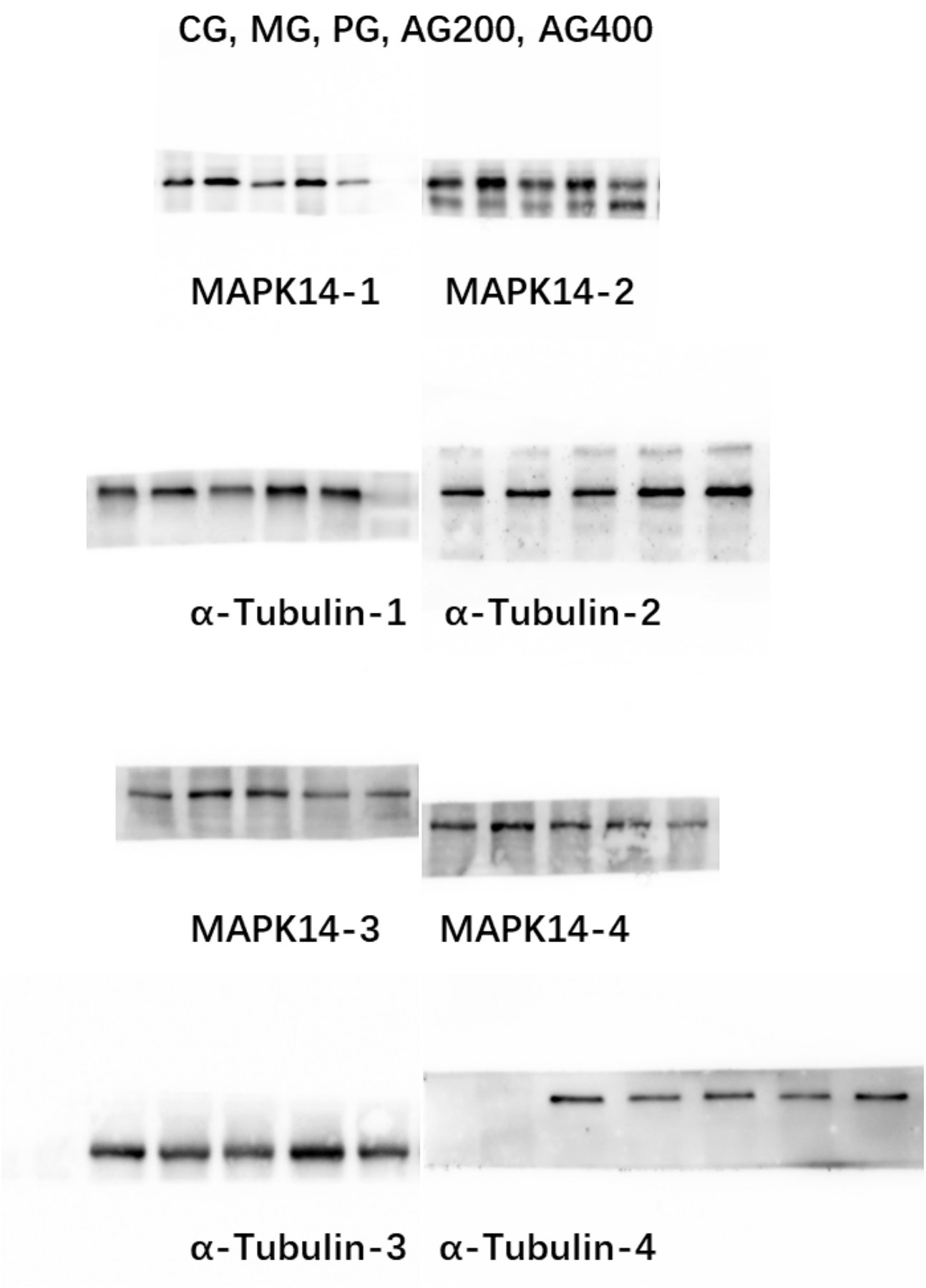


Figure S3. Raw images of Western blotting of MMP2, MMP9, MAP2K1, and MAPK14 in mice ankle joints from CG, MG, PG, AG200 and AG400 (n = 4).

Table S1. MS-based identification of the lipid molecular species detected in the present study

RT (min)	Lipids	Adduct	*m/z*	MS/MS	CG vs. MG			MG vs. AG200		MG vs. AG400	
					VIP	*P* value	FC	*P* value	FC	*P* value	FC
3.20	PC(O-32:3)/ PC(P-32:2)	$[M+H]^+$	714.5372	59.0494, 89.0602, 283.2625	1.54	1.2E-02	1.28	3.6E-03	0.76	1.5E-03	0.77
3.35	LPC(24:0)	$[M+H]^+$	608.4673	59.0501, 89.0594, 309.2754, 437.3180	1.00	2.3E-02	1.23	1.7E-04	0.73	1.2E-03	0.80
3.58	PC(O-34:4) /PC(P-34:3)	$[M+H]^+$	740.5528	89.0594, 309.2772, 723.5234	1.74	1.4E-02	1.24	2.8E-04	0.74	1.1E-03	0.79
5.10	PC(42:3)	$[M+H]^+$	868.6728	59.0524, 184.1753, 255.2302, 387.3093	1.99	1.2E-02	1.28	1.5E-03	0.75	8.4E-04	0.75
5.20	PC(O-40:4)/ PC(P-40:3)	$[M+H]^+$	824.6467	87.0436, 227.1986, 255.2299, 527.3050	2.11	1.2E-02	1.26	3.5E-04	0.74	5.7E-04	0.76
5.35	SM(34:1)	$[M+H]^+$	703.5755	87.0445, 184.0721, 641.5085	1.38	1.6E-03	1.66	7.0E-01	0.97	4.5E-01	0.93
5.90	PC(O-42:4)	$[M+H]^+$	852.6781	59.0489, 255.2321, 283.2636, 465.3186	1.61	1.7E-02	1.26	4.8E-04	0.74	5.4E-04	0.75
6.02	PC(O-44:5)	$[M+H]^+$	878.6935	89.0628, 227.1992, 309.2810, 470.3211	1.13	1.2E-02	1.28	9.6E-04	0.75	7.8E-04	0.75
6.23	PC(32:0)	$[M+H]^+$	734.5702	64.9773, 86.0947, 184.0714, 482.3289	2.36	1.6E-04	1.79	7.6E-02	0.86	1.7E-02	0.79
7.65	DG(36:5)	$[M+H]^+$	615.4964	59.0491, 129.0924, 337.9666	0.90	1.1E-02	1.30	3.5E-04	0.73	1.2E-04	0.67
7.68	SM(42:2)	$[M+H]^+$	813.6845	184.0722, 413.2722	1.29	2.0E-04	2.19	2.4E-01	0.92	5.7E-01	1.04
7.73	DG(38:6)	$[M+H]^+$	641.5122	89.0604, 321.3859	1.00	1.1E-02	1.36	1.8E-03	0.73	1.5E-03	0.68
7.93	Cer(38:0)	$[M+H]^+$	596.5993	282.2781, 284.2922	0.37	5.5E-03	1.27	3.8E-04	0.77	3.5E-04	0.77
9.43	PA(32:1)	$[M+H]^+$	647.4608	59.0497, 103.0750, 467.3161	1.26	1.7E-02	1.18	3.9E-04	0.80	1.4E-04	0.79
11.20	TG(50:4)	$[M+NH_4]^+$	844.7404	109.1020, 219.2095, 549.4852, 573.4881, 599.4857	3.35	1.2E-02	1.24	4.6E-03	0.85	9.7E-04	0.81
11.43	TG(51:4)	$[M+NH_4]^+$	858.7553	59.0563, 311.2563, 559.4631, 573.4844, 587.4983	1.27	1.0E-02	1.33	4.1E-02	0.83	4.1E-02	0.83
11.47	TG(46:1)	$[M+NH_4]^+$	794.7248	95.0846, 495.4351, 521.451, 549.4884	2.59	1.2E-02	1.47	3.1E-01	0.91	2.2E-02	0.79
11.52	TG(53:5)	$[M+NH_4]^+$	884.7693	123.1154, 165.1631, 335.2586, 587.5001	1.28	8.0E-03	1.36	4.1E-02	0.83	4.4E-02	0.83
11.53	TG(48:2)	$[M+NH_4]^+$	820.7407	57.0699, 265.2564, 523.4703, 549.4888, 575.5013	5.00	2.8E-03	1.42	4.2E-01	0.94	2.9E-02	0.81
11.60	TG(56:7)	$[M+NH_4]^+$	922.7875	95.0857, 273.2581, 577.5193, 599.5029, 625.5220	1.17	2.0E-02	1.21	2.6E-01	0.91	8.3E-03	0.72
11.60	TG(58:8)	$[M+NH_4]^+$	948.8030	247.2081, 601.5278, 651.5315, 875.7061	1.23	1.0E-03	1.32	1.3E-01	0.89	6.8E-03	0.77
11.68	TG(47:1)	$[M+NH_4]^+$	808.7377	57.0682, 115.0726, 451.3367, 509.4581, 537.4882, 565.5155	1.57	2.1E-05	1.37	6.6E-03	0.87	4.1E-04	0.83
11.80	TG(46:0)	$[M+NH_4]^+$	796.7402	57.0702, 257.2394, 523.4789, 552.5037	1.95	4.7E-05	1.51	1.6E-04	0.82	5.8E-05	0.77
11.80	TG(53:4)	$[M+NH_4]^+$	886.7876	263.2414, 327.2877, 589.5221, 601.5225	2.31	6.0E-03	1.45	4.3E-02	0.83	4.3E-02	0.82
11.82	TG(48:1)	$[M+NH_4]^+$	822.7573	57.0710, 311.2504, 549.4816, 551.4954	6.20	1.1E-04	1.82	3.2E-01	0.93	6.0E-03	0.78
11.83	TG(58:7)	$[M+NH_4]^+$	950.8191	89.0589, 285.2180, 317.2479, 627.5298, 655.5679	1.72	1.3E-04	1.34	1.4E-01	0.91	4.9E-03	0.82
11.93	TG(53:3)	$[M+NH_4]^+$	888.8033	95.0858, 591.5385, 603.5364, 617.5541	4.56	1.6E-04	1.51	2.0E-02	0.87	6.8E-03	0.83
11.97	TG(48:0)	$[M+NH_4]^+$	824.7732	59.0494, 495.4318, 535.4753, 552.5039	3.10	1.3E-05	1.68	2.5E-05	0.74	5.6E-05	0.70
5.25	PA(P-42:4)	$[M-H]^-$	763.5653	253.2146, 703.5424	1.69	1.1E-03	2.30	5.4E-01	0.94	8.3E-01	1.02
5.49	PE(40:8)	$[M-H]^-$	786.5107	241.0559, 328.1448	1.13	4.3E-02	1.29	5.6E-02	0.85	3.2E-01	0.91

5.65	PS(40:6)	$[M-H]^-$	834.5303	78.9634, 465.2479, 747.4771	2.74	1.9E-03	1.59	5.3E-02	0.77	2.3E-03	0.71
5.70	PS(41:5)	$[M-H]^-$	850.5623	59.0121, 255.2346, 506.3257, 792.5652	4.25	4.9E-02	1.23	3.3E-03	0.79	8.0E-03	0.80
5.70	PI(38:4)	$[M-H]^-$	885.5507	151.0651, 241.0197, 283.2698, 581.3164, 799.4825	4.01	7.0E-03	1.32	4.4E-03	0.80	4.6E-02	0.85
5.77	PI(36:2)	$[M-H]^-$	861.5511	409.2314, 789.5355	1.33	3.6E-02	1.32	3.6E-02	0.81	6.8E-02	0.82
5.89	PS(36:2)	$[M-H]^-$	786.5327	328.1448, 398.3309, 712.4988, 728.5265	1.42	2.2E-02	1.68	2.2E-01	0.78	8.0E-01	1.03
5.89	PS(39:3)	$[M-H]^-$	826.5620	140.0099, 255.2355, 283.2663, 506.3617, 715.5089	3.11	5.9E-03	1.20	2.6E-03	0.84	1.1E-01	0.89
5.92	PE(38:6)	$[M-H]^-$	762.5104	196.0435, 304.2463, 329.2524, 452.2850, 482.2645	2.67	1.1E-02	1.25	1.1E-02	0.85	9.4E-03	0.83
6.04	PE(40:7)	$[M-H]^-$	788.5259	152.9933, 419.2571, 701.5267	2.82	4.9E-02	1.18	2.1E-03	0.83	3.0E-03	0.80
6.29	PE(O-38:7)/ PE(P-38:6)	$[M-H]^-$	746.5155	78.9621, 140.0061, 196.0357, 282.2614, 303.2394, 329.2543.462.3122	2.49	4.9E-03	1.18	9.6E-06	0.80	2.0E-04	0.79
6.29	PI(36:1)	$[M-H]^-$	863.5660	56.0194, 96.9607	1.01	1.7E-02	1.50	4.2E-01	0.93	3.0E-02	0.80
6.39	PE(P-40:7)	$[M-H]^-$	772.5311	112.9837, 355.2584, 440.3079	1.66	2.7E-02	1.21	2.3E-03	0.78	2.8E-03	0.75
6.42	PS(41:3)	$[M-H]^-$	854.5891	96.9620, 283.2685, 305.2548, 795.5634	1.44	2.7E-02	1.14	2.1E-04	0.76	3.8E-04	0.73
6.47	PE(O-36:5) /PE(P-36:4)	$[M-H]^-$	722.5157	112.9896, 305.2560, 443.2293	2.03	3.2E-02	1.14	4.1E-05	0.80	1.3E-03	0.80
6.57	PE(O-38:6)/ PE(P-38:5)	$[M-H]^-$	748.5312	278.2246, 301.2233, 436.2922	2.27	3.0E-02	1.17	2.2E-03	0.79	1.4E-02	0.82
6.69	PE(O-36:4) /PE(P-36:3)	$[M-H]^-$	724.5317	159.0703, 281.2542, 463.3244	1.07	3.0E-02	1.18	3.1E-03	0.80	1.1E-02	0.82
6.69	PE(40:6)	$[M-H]^-$	790.5399	112.9862, 283.2628, 559.3010	4.13	1.5E-04	1.35	9.2E-03	0.84	1.7E-02	0.83
6.75	PE(34:1)	$[M-H]^-$	716.5267	68.9961, 112.9857, 136.117	1.84	1.7E-04	1.37	2.7E-05	0.81	3.6E-04	0.79
6.87	PE(38:4)	$[M-H]^-$	766.5416	112.9838, 196.0287, 283.2687, 303.2284, 480.3210, 633.4822	2.78	1.5E-02	1.19	8.0E-04	0.79	5.9E-03	0.82
7.05	PE(P-40:6)	$[M-H]^-$	774.5460	283.2546, 327.2401, 464.3232	1.95	6.5E-03	1.19	1.0E-04	0.79	3.2E-04	0.76
7.15	PE(O-34:2)/ PE(P-34:1)	$[M-H]^-$	700.5320	184.1088, 196.1561, 309.1766	2.52	1.6E-04	1.39	1.9E-02	0.84	2.8E-02	0.87
7.17	PE(38:3)	$[M-H]^-$	768.5536	112.9853, 353.1426, 564.5161	1.22	1.1E-03	1.30	7.8E-03	0.81	1.2E-02	0.82
7.24	PE(O-38:5)/ PE(P-38:4)	$[M-H]^-$	750.5471	303.2283, 418.2845, 676.5150	2.00	8.2E-03	1.17	2.0E-04	0.79	2.1E-03	0.81
7.27	PS(39:0)	$[M-H]^-$	832.6093	89.0286, 423.2612	2.04	2.7E-02	1.16	1.4E-03	0.80	5.3E-03	0.80
8.72	PS(43:0)	$[M-H]^-$	888.6714	146.9666, 669.5148	1.07	2.6E-03	1.30	3.9E-03	0.83	1.9E-01	0.91

FC: Fold Change, means raw abundance of group (2)/group (1), > 1 or < 1 means increased or decreased, respectively.

PC: Phosphatidylcholine, PC-(O/P): Plasmalogen, PA: Phosphatidic acid, SM: Sphingomyelin, Cer: Ceramide, DG: Diacylglycerol, TG: Triacylglycerol, PE: Phosphatidylethanolamine, PI: Phosphatidylinositol, PS: Phosphatidylserine.

Table S2. Chemical similarity enrichment analysis of differential lipids

Cluster name	Cluster size	*p*-value	FDR	Altered lipids	Increased	Decreased	Increased ratio
triglycerides	14	2.1E-12	1.5E-11	14	14	0	1
phosphatidylethanolamines	10	1.4E-08	4.9E-08	10	10	0	1
phosphatidylserines	7	3.2E-06	4.4E-06	7	7	0	1
phosphatidylcholines	6	0.000011	0.000012	6	6	0	1
plasmalogens	5	2.4E-08	5.7E-08	5	5	0	1
sphingolipids	3	2.2E-07	3.8E-07	3	3	0	1
phosphatidylinositols	3	0.000047	0.000047	3	3	0	1

p-value is the result of the Kolmogorov Smirnov test evaluating how significant difference a metabolite cluster was represented by chance. FDR is the Benjamini Hochberg corrected *p* value. The Increased or Decreased shows the numbers of increased or decreased significant compounds in a cluster. The Increased ratio means increased compounds/total altered metabolites.

Pathway	Total	Hits	Raw *p*	Holm adjust	FDR	Impact
Glycerophospholipid metabolism	36	9	5.9E-13	4.9E-11	4.9E-11	0.4667
Glycerolipid metabolism	16	4	5.8E-06	4.8E-04	2.4E-04	0.21775
Phosphatidylinositol signaling system	28	3	1.5E-03	1.2E-01	4.1E-02	0.12464
Glycosylphosphatidylinositol (GPI)-anchor biosynthesis	14	2	5.9E-03	4.8E-01	1.2E-01	0.00399
Inositol phosphate metabolism	30	2	2.6E-02	1.0E+00	3.7E-01	0.0777
Sphingolipid metabolism	21	2	1.3E-02	1.0E+00	2.2E-01	0.26978
Linoleic acid metabolism	5	1	4.2E-02	1.0E+00	5.1E-01	0
alpha-Linolenic acid metabolism	13	1	1.1E-01	1.0E+00	1.0E+00	0
Arachidonic acid metabolism	36	1	2.7E-01	1.0E+00	1.0E+00	0
Ether lipid metabolism	20	1	1.6E-01	1.0E+00	1.0E+00	0.18072

Table S3. Disturbed metabolic pathways in gouty arthritis

The Total is the total number of compounds in the metabolic pathway. The Hits is the actually matched number from the user uploaded data. The Raw *p* is the original *p* value calculated from the enrichment analysis. The Holm *p* is the *p* value adjusted by Holm-Bonferroni method. The FDR is the *p* value adjusted using False Discovery Rate. The Impact is the pathway impact value calculated from pathway topology analysis.

Table S4. Anthocyanins identified by UPLC-Q-TOF-MS from LR

Peak No.	RT (min)	Identification	Short name	*m/z*	Formula	MS/MS
1	3.827	petunidin 3-rutinoside-5-glucoside	Petunidin 1	787.2293	$C_{34}H_{42}O_{21}$	317/479/625
2	4.260	petunidin-3-O-glucoside-5-O-glucoside	Petunidin 2	641.1723	$C_{28}H_{33}O_{17}$	479/317
3	6.028	petunidin-3-O-glucoside	Petunidin 3	479.1175	$C_{22}H_{23}O_{12}$	317
4	7.946	petunidin-3-O-[6-O-(4-O-(4-O-(β-D-glucopyranosyl)-p-coumaroyl)-α-L-rhamnopyranosyl)-β-D-glucopyranoside]-5-O-[β-D-glucopyranoside]	Petunidin 4	1095.3152	$C_{49}H_{58}O_{28}$	317/479/933
5	11.847	petunidin-3-O-[6-O-(4-O-p-caffeoyl-α-L-rhamnopyranosyl)-β-D-glucopyranoside]-5-O-[β-D-glucopyranoside]	Petunidin 5	949.2647	$C_{43}H_{50}O_{24}$	317/479/787
6	12.057	delphinidin-3-O-[6-O-(4-O-p-coumaroyl-α-L-rhamnopyranosyl)-β-D-glucopyranoside]-5-O-[β-D-glucopyranoside]	Delphinidin 1	919.2475	$C_{42}H_{47}O_{23}$	303/465/757
7	12.232	petunidin-3-O-p-coumaroylrutinoside-5-O-glucoside	Petunidin 6	933.2661	$C_{43}H_{48}O_{23}$	317/479/771
8	14.332	delphinidin-3-O-(p-coumaroyl)-glucoside	Delphinidin 2	611.1605	$C_{27}H_{30}O_{16}$	303
9	15.333	petunidin-3-O-[6-O-(4-O-cis-p-coumaroyl-α-L-rhamnopyranosyl)-β-D-glucopyranoside]-5-O-[β-D-glucopyranoside]	Petunidin 7	933.2661	$C_{43}H_{48}O_{23}$	317/479/771
		petunidin-3-O-[6-O-(4-O-trans-p-coumaroyl-α-L-rhamnopyranosyl)-β-D-glucopyranoside]-5-O-[β-D-glucopyranoside]	Petunidin 8	933.2661	$C_{43}H_{48}O_{23}$	317/479/771
10	16.05	petunidin-3-O-p-coumaroyl-rutinoside-5-O-glucoside	Petunidin 9	933.2661	$C_{43}H_{48}O_{23}$	317/479/771
11	17.851	malvidin-3-O-[6-O-(4-O-p-coumaroyl-α-L-rhamnosyl)-β-D-glucopyranoside]-5-O-β-D-glucopyranoside	Malvidin 1	947.2821	$C_{44}H_{50}O_{23}$	331/493/785
12	21.002	petunidin-3-O-(p-coumaroyl)-rutinoside	Petunidin 10	771.2011	$C_{37}H_{39}O_{18}$	317/479

Table S5. The typical components and related targets in LR anthocyanins

Components	Formula	PubChem ID	Targets counts	Targets
petunidin-3-rutinoside-5-glucoside	$C_{34}H_{42}O_{21}$	44256960	17	Abcb1b, Abcc1, Ache, Akt1, Csnk2a1, Egfr, F2, Hsd17b2, Insr, Maoa, Mmp2, Mmp9, Oprm1, Pik3cg, Pla2g1b, Pparg, Ptgs2
petunidin-3-O-glucoside-5-O-glucoside	$C_{28}H_{33}O_{17}$	75184857	18	Abcb1b, Abcc1, Ache, Akt1, Csnk2a1, Egfr, F2, Hsd17b2, Insr, Maoa, Mmp2, Mmp9, Oprm1, Pik3cg, Pla2g1b, Pparg, Ptgs2, Slc10a2
petunidin-3-O-glucoside	$C_{22}H_{23}O_{12}$	443651	18	Abcb1b, Abcc1, Ache, Akt1, Csnk2a1, Egfr, F2, Hsd17b2, Insr, Maoa, Mmp2, Mmp9, Oprm1, Pik3cg, Pla2g1b, Pparg, Ptgs2, Slc10a2
petunidin-3-O-[6-O-(4-O-(4-O-(β-D-glucopyranosyl)-p-coumaroyl)-α-L-rhamnopyranosyl)-β-D-glucopyranoside]-5-O-[β-D-glucopyranoside]	$C_{49}H_{58}O_{28}$	44256974	5	Abcc1, Ache, Egfr, Mmp2, Ptgs2
petunidin-3-O-[6-O-(4-O-p-caffeoyl-α-L-rhamnopyranosyl)-β-D-glucopyranoside]-5-O-[β-D-glucopyranoside]	$C_{43}H_{48}O_{24}$	44256970	5	Abcc1, Ache, Egfr, Mmp2, Ptgs2
delphinidin-3-O-[6-O-(4-O-p-coumaroyl-α-L-rhamnopyranosyl)-β-D-glucopyranoside]-5-O-[β-D-glucopyranoside]	$C_{42}H_{46}O_{23}$	138319216	17	Abcc1, Ace, Ache, Casp1, Csnk2a1, Egfr, F2, Hmgcr, Hsp90aa1, Mme, Mmp2, Oprm1, Plau, Ptgs1, Ptgs2, Ren1, Slc10a2
petunidin-3-O-p-coumaroyl-rutinoside-5-glucoside	$C_{43}H_{48}O_{23}$	9897848	5	Abcc1, Ache, Egfr, Mmp2, Ptgs2
delphinidin-3-O-(p-coumaroyl)-glucoside	$C_{27}H_{30}O_{16}$	15922818	11	Abcc1, Ache, Egfr, F2, Insr, Mmp2, Oprm1, Pik3cg, Plau, Ptgs2, Raf1
petunidin-3-O-[6-O-(4-O-cis-p-coumaroyl-α-L-rhamnopyranosyl)-β-D-glucopyranoside]-5-O-[β-D-glucopyranoside]	$C_{43}H_{48}O_{23}$	9897848	5	Abcc1, Ache, Egfr, Mmp2, Ptgs2
petunidin-3-O-[6-O-(4-O-trans-p-coumaroyl-α-L-rhamnopyranosyl)-β-D-glucopyranoside]-5-O-[β-D-glucopyranoside]	$C_{43}H_{48}O_{23}$	134722739	5	Abcc1, Ache, Egfr, Mmp2, Ptgs2
petunidin-3-O-p-coumaroyl-rutinoside-5-glucoside	$C_{43}H_{48}O_{23}$	44256967	5	Abcc1, Ache, Egfr, Mmp2, Ptgs2
malvidin-3-O-[6-O-(4-O-p-coumaroyl-α-L-rhamnosyl)-β-D-glucopyranoside]-5-O-β-D-glucopyranoside	$C_{44}H_{50}O_{23}$	44257010	5	Abcc1, Ache, Egfr, Mmp2, Ptgs2
petunidin-3-O-(p-coumaroyl)-rutinoside	$C_{37}H_{39}O_{18}$	44256964	6	Abcc1, Ache, Egfr, F2, Mmp2, Ptgs2

Table S6. Functional enrichment results of potential targets

Pathways	Potential targets	Counts	*p* value	FDR
Pathways in cancer	CSF1R, MAP2K1, HSP90AA1, MMP2, BRAF, PTGS2, MMP9, PIK3CG, MTOR, EGFR, PIK3CA, KIT, ABL1, AKT1, MAPK1, PPARG, RAF1	17	1.22E-09	5.01E-08
Ras signaling pathway	CSF1R, MAP2K1, FLT1, PLA2G1B, INSR, PIK3CG, EGFR, PIK3CA, KIT, ABL1, AKT1, MAPK1, RAF1	13	1.27E-08	1.07E-07
PI3K-Akt signaling pathway	CSF1R, MAP2K1, HSP90AA1, FLT1, INSR, PIK3CG, MTOR, EGFR, PIK3CA, KIT, AKT1, MAPK1, RAF1	13	1.35E-06	4.95E-06
Prostate cancer	MAP2K1, HSP90AA1, PIK3CA, AKT1, MAPK1, BRAF, RAF1, EGFR, PIK3CG, MTOR	10	3.13E-09	5.01E-08
FoxO signaling pathway	MAP2K1, PIK3CA, INSR, AKT1, MAPK1, BRAF, MAPK14, RAF1, EGFR, PIK3CG	10	1.29E-07	7.04E-07
Central carbon metabolism in cancer	MAP2K1, PIK3CA, KIT, AKT1, MAPK1, RAF1, EGFR, PIK3CG, MTOR	9	5.05E-09	6.10E-08
HIF-1 signaling pathway	MAP2K1, FLT1, PIK3CA, INSR, AKT1, MAPK1, EGFR, PIK3CG, MTOR	9	2.09E-07	9.71E-07
Sphingolipid signaling pathway	ABCC1, MAP2K1, PIK3CA, AKT1, MAPK1, FYN, MAPK14, RAF1, PIK3CG	9	9.44E-07	3.66E-06
VEGF signaling pathway	MAP2K1, PIK3CA, AKT1, MAPK1, MAPK14, PTGS2, RAF1, PIK3CG	8	8.17E-08	4.75E-07
Choline metabolism in cancer	MAP2K1, PIK3CA, AKT1, MAPK1, RAF1, EGFR, PIK3CG, MTOR	8	2.99E-06	8.96E-06
TNF signaling pathway	MAP2K1, PIK3CA, AKT1, MAPK1, MAPK14, PTGS2, MMP9, PIK3CG	8	4.98E-06	1.34E-05
cAMP signaling pathway	MAP2K1, PIK3CA, AKT1, MAPK1, BRAF, PPARA, RAF1, PIK3CG	8	2.24E-04	4.26E-04
AMPK signaling pathway	PIK3CA, INSR, AKT1, PPARG, HMGCR, PIK3CG, MTOR	7	1.47E-04	3.11E-04
MAPK signaling pathway	MAP2K1, AKT1, MAPK1, BRAF, MAPK14, RAF1, EGFR	7	4.91E-03	7.48E-03
mTOR signaling pathway	PIK3CA, AKT1, MAPK1, BRAF, PIK3CG, MTOR	6	3.29E-05	8.06E-05
Toll-like receptor signaling pathway	MAP2K1, PIK3CA, AKT1, MAPK1, MAPK14, PIK3CG	6	4.26E-04	7.48E-04
Arachidonic acid metabolism	PLA2G1B, LTA4H, PTGS2, PTGS1	4	1.88E-02	2.36E-02
NF-kappa B signaling pathway	CSNK2A1, PLAU, BTK, PTGS2	4	2.36E-02	2.85E-02
Ovarian steroidogenesis	INSR, HSD17B2, PTGS2	3	5.08E-02	5.84E-02

The Counts represent the total numbers of potential targets involved in the corresponding pathways. The *p* value is the original *p* value calculated from the enrichment analysis. The FDR is the *p* value adjusted using False Discovery Rate.

Table S7. Molecular docking results of active components from LR anthocyanins and target proteins

Short name	Akt1	Egfr	F2	Hsp90aa1	Insr	Map2k1	Mapk1	Mapk14	Mmp2	Mmp9	Mtor	Pik3ca	Pik3cg	Pparg	Ptgs2	Raf1
Petunidin 1	**-4.39**	-1.49	-2.92	-2.72	-0.53	-2.08	-1.7	-1.88	-2.91	-3.35	-2.73	-2.01	-0.01	-1.45	-1.65	-1.36
Petunidin 2	-3.39	-3.43	-3.92	-3.62	-1.87	-3.19	-2.96	-3.2	**-4.41**	**-4.24**	-2.98	-3.91	-2.34	-3.19	**-4.04**	-3.92
Petunidin 3	-3.84	-2.36	**-4.73**	-3.63	-1.7	**-4.3**	-1.81	-2.77	**-4.49**	**-4.08**	-3.79	-2.68	-1.82	-2.52	-2.46	-3.55
Petunidin 4	-2.29	-2.13	-2.38	-2.97	-1.05	-2.88	-2.08	-1.5	-3.82	-2.9	-2.73	-3.74	-0.03	-2.79	-2.07	-2.65
Petunidin 5	0.21	-2.28	-1.54	-2.42	1.19	-1.15	-0.44	-0.64	-3.09	-4.27	-1.96	-0.79	2.81	-0.15	0.34	-1.52
Delphinidin 1	-2.97	-1.51	-2.57	-1.87	-1.44	-1.42	-1.51	-1.27	-1.16	-2.42	-2.4	-0.74	-0.54	-0.62	-0.55	-0.97
Petunidin 6	0.48	1.2	1.98	0.61	1.8	1.42	1.54	1.09	1.24	-0.1	1.64	-1.04	1.95	2.08	3.28	2.51
Delphinidin 2	-3.21	-2.5	-3.7	-3.97	-1.02	**-5.47**	-0.67	-1.01	**-4.85**	**-4.13**	-2.21	-3.7	-1.26	-2.97	-1.53	-1.94
Petunidin 7	-2.04	-1.62	-2.62	**-4.58**	-2	-2.16	-3.45	-0.63	-2.62	-3.73	-3.87	-1.98	0.76	-1.1	-0.59	-1.93
Petunidin 8	-0.76	-2.79	**-4.66**	-3.17	-1.46	-2.4	-3.21	**-5.04**	**-5.12**	**-4.3**	-3.09	-2.51	-0.55	-2.3	-2.79	-3.6
Petunidin 9	0.48	1.2	1.98	0.61	1.8	1.42	1.54	1.09	1.24	-0.1	1.64	-1.04	1.95	2.08	3.28	2.51
Malvidin 1	1.91	2.52	1.26	-0.56	3.38	1.63	2.48	1.51	-0.16	-0.65	1.62	1.87	2.85	2.53	2.64	1.86
Petunidin 10	-3.22	**-4.39**	**-4.16**	**-4.17**	-2.48	**-5.07**	-3.03	-3.87	**-4.91**	**-5.13**	-3.82	**-4.73**	-1.39	**-4.1**	-3.65	-2.96

Grey: binding energy was higher than 0 kcal/mol, black: less than 0 kcal/mol, bold black: less than -4 kcal/mol (high binding activity between the compound and target protein receptor), bold red: less than -5 kcal/mol (ultra-high binding activity between the compound and target protein receptor).