A

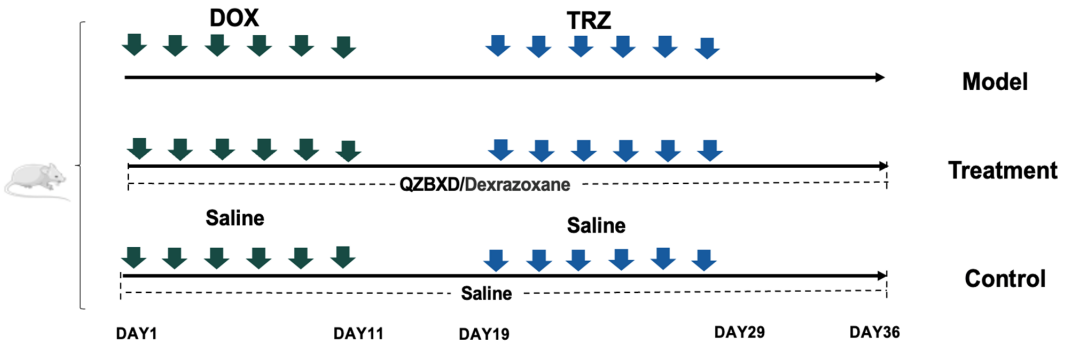

Figure S1 Experimental design of the animal studies.

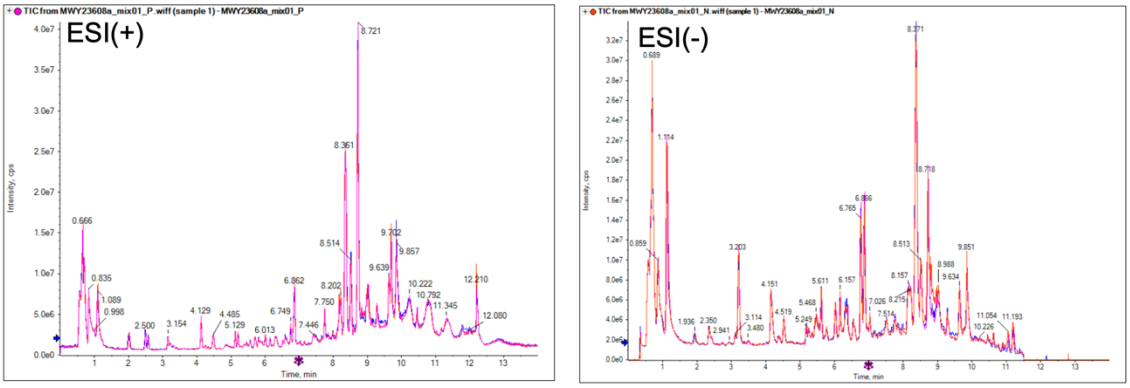

Figure S2. Overlapped chromatograms of total ions of quality control samples. ESI (+), positive-ion mode. ESI (-), negative-ion mode

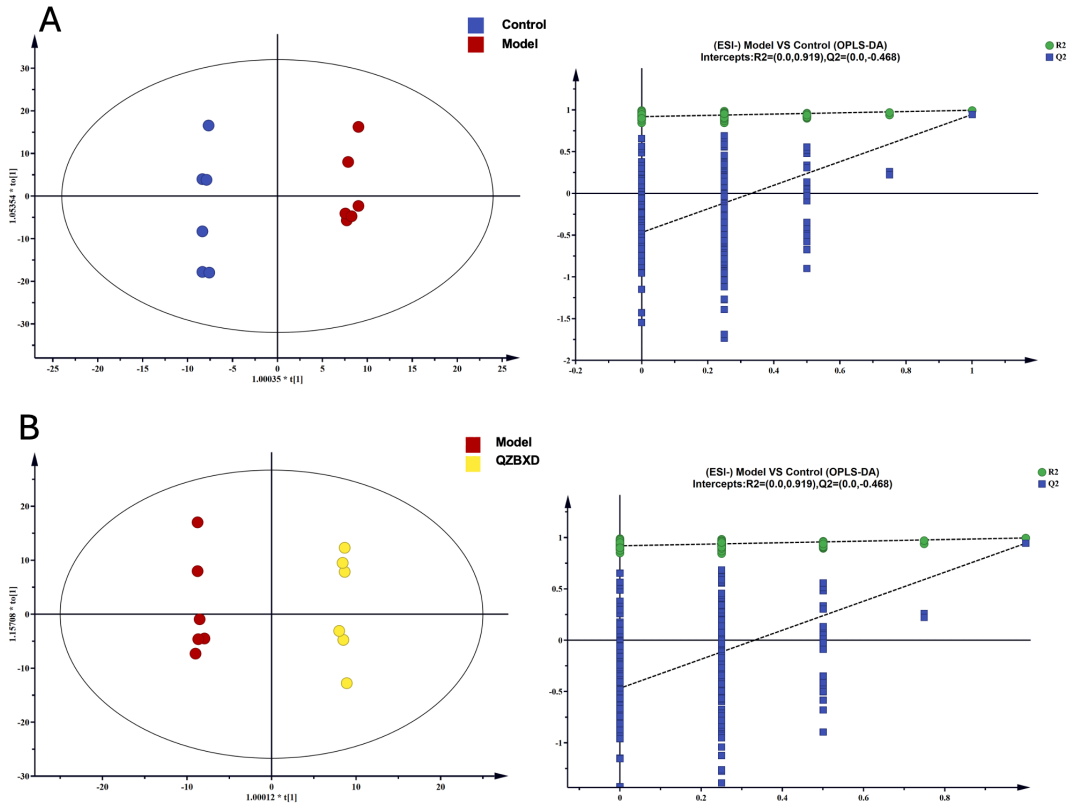

Figure S3 (A) Results of the OPLS-DA model using the data from the control vs model groups and the permutation tests of OPLS-D scatter. (B) Results of the OPLS-DA model using the data from the model vs QZBXD groups and the permutation tests of OPLS-D scatter.

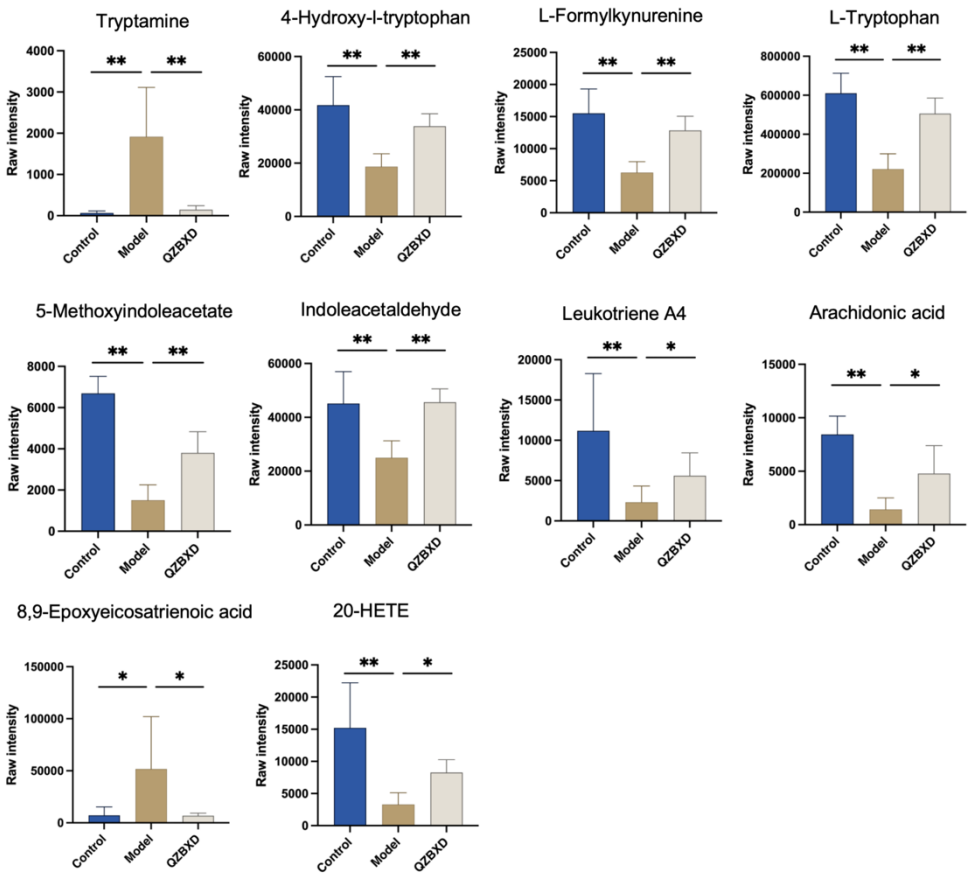

Figure S4 (A) The raw intensity values of 10 key differential metabolites in each group.

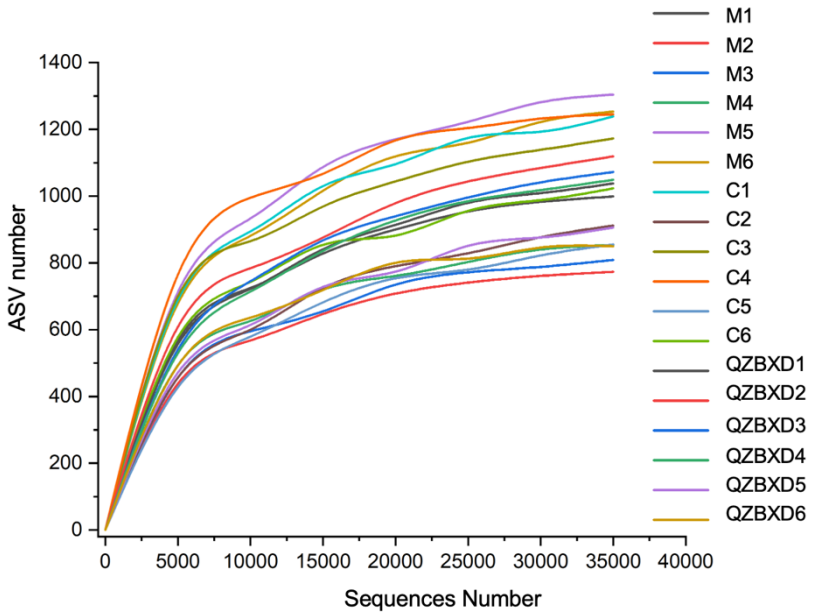

Figure S5 The rarefaction curve uses the microbial alpha diversity (α-diversity) index of each sample.

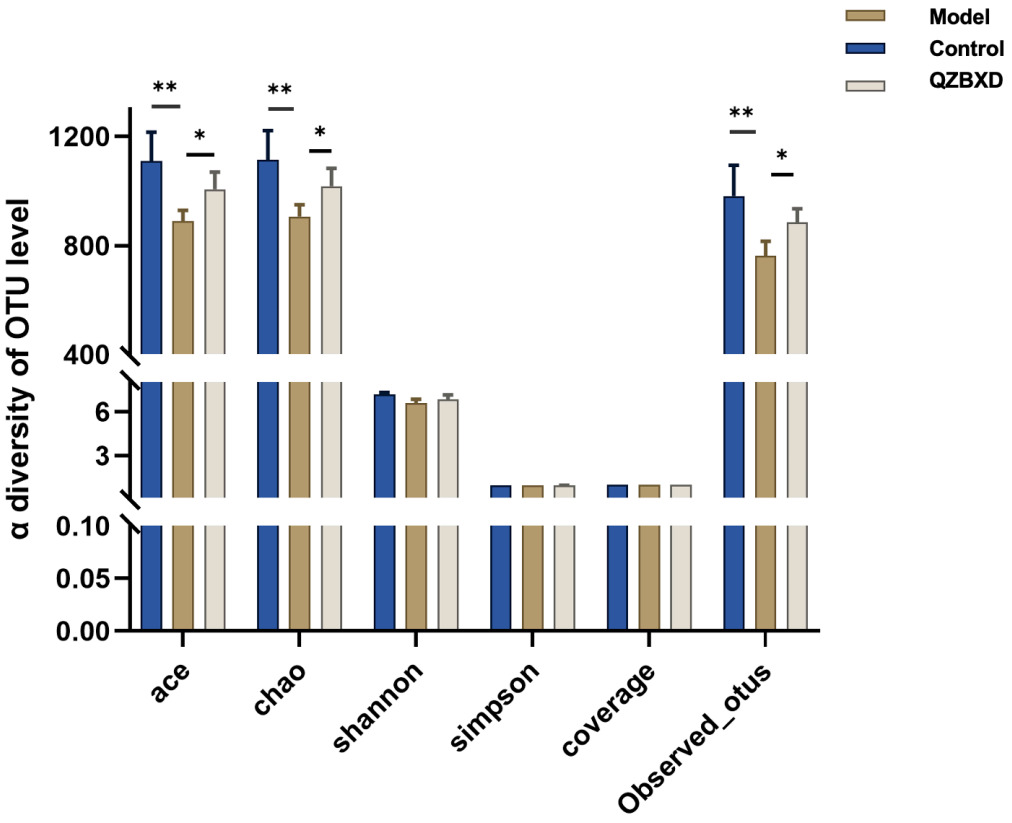

Figure S6 Reflecting the alpha diversity of the gut microbes in ace, Chao, Shannon, Simpson, coverage and Observed_otus index changes in each group

Table S1. UPLC gradient for component analysis of QZBXD

Time (min)	A (%)	B (%)	Flow (mL/min)
0.0	5	95	0.3
2.0	5	95	0.3
4.0	15	85	0.3
8.0	20	80	0.3
12.0	26	74	0.3
15.0	35	65	0.3
17.0	80	20	0.3
18.0	95	5	0.3
25.0	5	95	0.3
30.0	5	95	0.3

Mobile phase A: acetonitrile. Mobile phase B: 0.05% formic acid/water.

The column temperature was 30 ℃.

The loading volume for each sample was 1 μL.

Column：ACQUITY UPLC ®BEH-C18 Column（2.1 mm×100 mm，1.7 μm）

Table S2. UPLC gradient for plasma metabolomics analysis

Time (min)	A (%)	B (%)	Flow (mL/min)
0.0	95	5	0.4
11.0	10	90	0.4
12.0	10	90	0.4
12.1	95	5	0.4
14.0	95	5	0.4

Mobile phase A: 0.1% formic acid/water. Mobile phase B: 0.1% formic acid/acetonitrile

The column temperature was 40 ℃.

The loading volume for each sample was 2 μL.

Column：ACQUITY UPLC ®BEH-C18 Column（2.1 mm×100 mm，1.8 μm）

Table S3 The identified flavonoids compounds of QZBXD based on the UPLC-Q-TOF/MS- method.

No.	RT (Min)	Chemicals	Formula	Ion Mode	m/z (Measured)	m/z (Theoretical)	Error (ppm) ($\times 10^6$)	MS2 Fragments (*m/z*)	
1	21.614	Cryptotanshinone	C19H20O3	[M+H]+	297.1487	297.1485	0.67	251.1431、249.0917、209.0965、193.1020	a
2	5.419	Chlorogenic acid	C16H18O9	[M+H]+	355.1023	355.1024	-0.28	163.0394 145.0505 127.0389	a
3	13.275	Rosmarinic acid	C18H16O8	[M+H]+	361.0923	361.0918	1.38	352.2122 163.0388 135.0441 139.0392 117.0336	a
4	20.419	Przewaquinone A	C19H18O4	[M+H]+	311.1288	311.1278	3.21	293.2102 283.1332 279.1596	a
5	22.117	Tanshinone II A	C19H18O3	[M+H]+	295.133	295.1329	0.34	277.1230 249.1282 234.1025	a
6	20.423	Tanshinone II B	C19H18O4	[M+H]+	311.1287	311.1278	2.89	293.2117 285.1496 275.1599 191.1073	a
7	19.624	Astragaloside I	C41H68O14	[M+H]+	785.4768	785.4776	-1.02	473.3626 437.3414 419.3345 143.1068	b
8	20.414	Astragaloside II	C45H72O16	[M+H]+	869.4905	869.4893	1.38	689.4277 671.4173 654.4102 455.3537	b
9	10.591	Calycosin-7-O-β-D-glucoside	C22H22O10	[M+H]+	447.1285	447.1286	-0.22	311.1287 157.0492 285.0768 270.0534 253.0514	b
10	12.953	Malonyl calycosin-7-O-β-D-glucoside	C25H24O13	[M+H]+	533.1303	533.129	2.44	285.0751 270.0535	b
11	14.82	Ononin	C22H22O9	[M+H]+	431.1338	431.1337	0.23	269.0796	b
12	19.684	Formononetin	C16H12O4	[M+H]+	269.0808	269.0808	0.00	253.0506 237.0599 213.0926 197.0603 170.0736 137.0239	b

13	16.732	Isomucronulatol 7-O-beta-glucoside	C23H28O10	[M+H]+	465.177	465.1772	-0.43	315.0873 303.1240 279.1596 193.0874 167.0706 127.0392 133.0655	b
14	16.728	7,2'-Dihydroxy-3',4'-dimethoxyisoflavan	C17H18O5	[M+H]+	303.1237	303.1227	3.30	193.0874 181.0867 167.0705 123.0441 161.0601	b
15	16.095	astraperocarpan-3-O-Glc	C23H26010	[M+H]+	463.1603	463.1599	0.86	301.1076 297.0765 295.0615 127.0394	b
16	18.161	Malonylisoflavan	C26H30O13	[M+H]+	551.1781	551.1759	3.99	510.3297 416.3744 371.3168 324.2181	b
17	18.628	6″-O-Acetyl-Ononin	C24H24O10	[M+H]+	473.145	473.1442	1.69	397.1774 269.0817	b
18	17.648	Malonylastragalosi de Flavanone	C26H28O13	[M+NH4]+	567.1922	567.1946	-4.23	549.1623 301.1083 167.0708	b
19	18.161	Malonylisoflavan Glucoside	C26H30O13	[M+NH4]+	569.2085	569.2103	-3.16	515.1572 411.1449 369.1342 324.2181 167.0707	b
20	17.077	Malonylononin	C25H24O12	[M+H]+	517.134	517.1341	-0.19	499.1916 324.2183 169.0663	b
21	19.898	Astragaloside II	C43H70O15	[M+H]+	828.4741	828.4748	-0.84	630.4072 456.3669 438.3464 420.3393	b
22	8.178	2-Methoxycinnamal dehyde	C10H10O2	[M+H]+	163.0757	163.0754	1.84	149.0240 127.0392 131.0496	c
23	12.805	Pratensein-7-O-β-D-glucoside	C22H22O11	[M+H]+	463.1247	463.1235	2.59	364.2344 207.1021	c
24	6.49	Vanillic Acid	C8H8O4	[M+H]+	169.05	169.0495	2.96	151.0387 127.0391 109.0289	d
25	1.04	Adenine	C5H5N5	[M+H]+	136.0622	136.0618	2.94	118.0865 114.0917 104.0709	d
26	8.244	Lindleyine	C17H19NO3	[M+H]+	286.1434	286.1437	-1.05	269.1174 237.0920 175.0757 143.0494 107.0488	

27	8.739	Visnagin-2	C27H30O15	[M+H]+	595.1676	595.1657	3.19	577.1581 559.1464 337.0716 325.0716 295.0603	e
28	10.596	Spinacetin	C28H32O15	[M+H]+	609.1809	609.1814	-0.82	447.1280 411.1085 351.0865 327.0854 297.0762 285.0764	e
29	10.564	Isovitexin	C22H22O10	[M+H]+	447.1282	447.1285	-0.67	285.0766 270.0532 253.0497	e
30	12.615	6‴-Sinapoylspinacetin	C39H42O19	[M+H]+	815.2412	815.2393	2.33	695.1836 447.1235 351.0890 327.0876 207.0659 297.0574	e
31	12.974	6‴-Coumaroylspinacetin	C37H38O17	[M+H]+	755.2205	755.2182	3.05	625.1778 447.1309 429.1209 351.0901 327.0895	e
32	13.01	6‴-Feruloylspinacetin	C38 H40 O18	[M+H]+	785.2298	785.2287	1.40	665.1903 447.1307 429.1196 381.0991	
33	11.811	Senkyunolide J	C12H18O4	[M+H]+	227.1277	227.1277	0.00	209.1191 191.1064 163.1118 153.0553 117.0704 77.0384	
34	8.75	Kaempferol-3-O-Rutinoside	C27H30O15	[M+H]+	595.1677	595.1657	3.36	577.1575 559.1473 457.1154	e
35	11.867	Senkyunolide K	C12H16O3	[M+H]+	209.1175	209.1172	1.43	191.1074 179.0712 163.0388 127.0395	d
36	13.76	Senkyunolide I	C12H16O4	[M+H]+	225.1128	225.1121	3.11	207.1020 189.096	d
37	13.774	3-Butenyl-4-Hydroxyphthalide	C12H14O3	[M+H]+	207.102	207.1016	1.93	189.0912 133.0652	d f
38	14.578	Senkyunolide F	C12H14O3	[M+H]+	207.1021	207.1016	2.41	189.0911 123.0412	d f
39	20.624	Senkyunolide A	C12H16O2	[M+H]+	193.1222	193.1223	-0.52	175.1121 147.1162 137.0595	d f
40	19.687	E-Ligustilide	C12H14O2	[M+H]+	191.1067	191.1067	0.00	173.0974 145.070 117.0731 91.0536	d f
41	21.087	Z-Ligustilide	C12H14O2	[M+H]+	191.1068	191.1067	0.52	173.0966 161.1131 145.1017 117.0700 130.0785	d f

42	19.609	3-Butylidenephthalide	C12H14O2	[M+H]+	189.0911	189.091	0.53	147.0439 152.0624 143.0856 133.0286 128.0625 129.0355、105.0337、77.0384	d f
43	21.934	Angelicide	C24H28O4	[M+H]+	381.2073	381.206	3.41	343.3320 280.2693 191.1072 173.0970	d f
44	13.799	Senkyunolide H	C12H1604	[M+H]+	225.1128	225.1121	3.11	207.1015 163.0402 127.0395	d f
45	14.331	Senkyunolide D	C12H14O4	[M+H]+	223.0974	223.0965	4.03	205.0876 177.0543	d f
46	19.687	Senkyunolide G	C12H16O3	[M+H]+	209.1173	209.1172	0.48	191.1064 149.0283 135.0448 128.0393 91.0544 85.0656 79.0542	d f
47	17.384	Ligustilide	C12H12O2	[M+H]+	189.0908	189.091	-1.06	161.0962 149.0239 127.0392	d f
48	21.069	Levistilide A	C24H28O4	[M+H]+	381.2078	381.206	4.72	191.1073 173.0968 135.0345 149.0610	d f
49	21.96	Senkyunolide Q	C16H22O4	[M+H]+	279.1595	279.159	1.79	149.0238 205.0868 127.0395	d f
50	3.701	dihydroeugenol	C10H14O2	[M+Na]+	189.0872	189.0886	-7.40	91.0544，118.0658	d f
51	1.251	Citric acid monohydrate	C6H8O7	[M-H]-	191.0215	191.0197	9.42	173.0107 147.0309 133.0154 128.0365	a
52	0.945	Disaccharide	C12H22O11	[M-H]-	341.11	341.1089	3.22	277.0351 195.0525 179.0576	a
53	1.72	Danshensu	C9H10O5	[M-H]-	197.0453	197.0455	-1.01	191.0212 179.0574 135.0463	a
54	7.22	Caffeic acid	C9H8O4	[M-H]-	179.036	179.035	5.59	135.0462 121.0304	a f
55	6.474	Vanillic acid	C8H8O4	[M-H]-	167.0363	167.035	7.78	123.0461 96.9707	a f
56	4.076	3,4-Dihydroxybenzaldehyde	C7H6O3	[M-H]-	137.0255	137.0244	8.03	108.0224 96.9701 78.9596 53.0397 41.0035	a
57	10.292	ferulic acid	C10H10O4	[M-H]-	193.0514	193.0506	4.14	178.0288 149.0618	a f

								134.0384	
58	9.783	Salvianolic acid F	C17H14O6	[M-H]-	313.0742	313.0718	7.67	269.0842 247.1211 209.0470	a
59	10.884	Salvianolic acid U	C27H22O12	[M-H]-	537.1086	537.1038	8.94	493.1176	a
60	11.3	Salvianolic acid T	C27H22O12	[M-H]-	537.1081	537.1038	8.01	493.1088 473.1707 441.1807 339.0517	a
61	12.185	Salvianolic acid H/I	C27H18O12	[M-H]-	537.1081	537.1038	8.01	487.0928 339.054 309.1586	a
62	13.718	Lithospermic acid	C27H18O12	[M-H]-	537.1084	537.1038	8.56	493.1184 295.0632	a
63	14.951	Salvianolic acid J	C27H18O13	[M-H]-	537.1057	537.1038	3.54	493.1182 451.1291	a
64	14.574	Salvianolic acid B	C36H30O16	[M-H]-	717.1505	717.1461	6.14	358.0718 295.0638 519.0976 493.1185 339.0528 321.0417	a
65	15.758	Isomers of Salvianolic Acid B	C36H30O17	[M-H]-	717.1501	717.1461	5.58	279.0317 295.0629 519.0976 321.0429 295.0636	a
66	17.218	Salvianolic acid C	C26H20O10	[M-H]-	491.1021	491.0984	7.53	311.0585 293.0477 249.0572	a
67	21.216	Neocryptotanshinone	C19H22O4	[M-H]-	313.1471	313.1445	8.30	293.2144 249.1371 179.0759	a
68	11.588	Salviaflaside	C24H26O13	[M-H]-	521.1342	521.1301	7.87	359.0803 323.0803 197.0478 161.0257	a
69	12.415	Tangshenoside V	C21H26O12	[M-H]-	469.1379	469.1351	5.97	325.0984 119.0512 163.0414	g
70	9.713	Tangshenoside I	C29H42O18	[M-H]-	677.2323	677.2298	3.69	585.2453 461.1711 385.1174	g
71	12.993	Azelaic acid	C9H16O4	[M-H]-	187.099	187.0976	7.48	179.0767 125.0982 96.9703	g
72	18.864	9,12,13-Trihydroxy-10,15-octadecadienoic Aci	C18H32O5	[M-H]-	327.22	327.2177	7.03	293.0482 229.1453 211.1345	g
73	19.48	9,12,13-	C18H34O5	[M-H]-	329.2349	329.2333	4.86	229.1462 211.1355	g

		Trihydroxy-10-octadecenoic Acid						171.1039	
74	2.304	protocatechuic acid	C7H6O4	[M-H]-	153.0206	153.0193	8.50	109.0302 108.0225 91.0191	d
75	10.437	camellianin B	C32 H38 O19	[M-H]-	725.199	725.1935	7.58	637.1815 469.1397 539.1240 193.0522	e
76	19.63	Astragaloside VI	C47H78O19	[M-H]-	946.57	946.5708	-0.85	784.4614 607.0934 489.3685	b
77	20.398	Isoscoparin-7-O-β-D-glucoside	C23H28O10	[M-H]-	463.1642	463.161	6.91	407.1385 301.1139 286.0879 271.0651	b
78	16.748	Glycine-15N	C16H12O5	[M-H]-	283.0631	283.0612	6.71	268.0399 239.0366 211.0416 184.0540	b
79	16.273	Formononetin	C16H12O4	[M-H]-	267.0686	267.0663	8.61	252.0445 223.0416 195.0469	b
80	19.689	Astragaloside II	C43H70O15	[M+COOH]–	871.4767	871.4713	6.20	825.4713 765.4488 329.2360	b
81	19.58	Astragaloside III	C41H68O14	[M+COOH]–	829.4646	829.461	4.34	783.4606 621.4064	b
82	19.568	Wogonin	C16H12O5	[M-H]-	283.0645	283.0635	3.53	268.0396 268.0388	b
83	10.574	Salvianolic acid C	C26H20O10	[M-H]-	491.1021	491.0984	7.53	311.0585 293.0477 249.0572	g

“*” indicates the compounds were identified by reference materials.

a, Radix Astragali; b, Astragalus; c, Cinnamomi Ramulus; d, Rhizoma Chuanxiong; e, Spine Date Seed; f, Angelica sinensis; g, Codonopsis Radix