Supporting information

Comparative Metabolomic Analysis Reveals Global Cadmium Stress Response of *Lactobacillus plantarum* Strains

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List of supplemental information

Supplemental Figure S10. Cross-validation of the OPLS-DA model of CCFM8610(Cd)/8610(0).

Supplemental Figure S11. Cross-validation of the OPLS-DA model of CCFM191(Cd)/CCFM191(0).

Table S1 Differentially synthesized metabolites between *Lactobacillus plantarum* CCFM8610 and CCFM191 in Cd-free conditions

M/Z[a]	R.T. (min)[b]	Ion mode	Metabolites	Adduct[c]	Δ m[d]	VIP	*P* value[e]	Fold change[f]
377.086	0.698	NEG	D-Lactose	[M+Cl]-	0.00080	23.85	9.8E-20	0.05
179.056	0.714	NEG	D-Fructose	[M-H]-	-0.00010	9.62	7.4E-14	7.70
446.187	0.735	POS	b-D-Xylopyranosyl-(1->4)-a-L-rhamnopyranosyl-(1->2)-L-arabinose	$[M+NH_4]+$	0.00230	2.50	3.5E-13	0.07
593.195	0.743	NEG	punaglandin	[M+Cl]-	0.00310	2.11	2.1E-12	0.09
630.223	1.096	NEG	7-Sulfocholyltaurine	[M+Cl]-	0.00620	2.69	3.8E-12	0.36
365.106	0.701	POS	Sucrose	[M+Na]+	0.00010	5.63	2.6E-11	0.06
387.116	0.670	NEG	Fructoselysine 6-phosphate	[M-H]-	-0.00180	4.06	7.8E-11	0.15
431.109	0.740	NEG	TyrMe-Asp-OH	[M-H]-	-0.00070	2.35	1.5E-10	0.16
784.149	4.370	NEG	Flavin adenine dinucleotide (FAD)	[M-H]-	-0.00080	3.50	7.7E-10	2.03
146.046	0.732	NEG	L-Glutamate	[M-H]-	0.00020	7.14	1.2E-09	1.88
381.079	0.691	POS	Dihydrocaffeic acid 3-O-glucuronide	[M+Na]+	0.00010	4.28	3.6E-09	0.09
513.025	0.706	NEG	Fucofuroeckol B	[M+Cl]-	0.00250	2.33	5.6E-09	0.15
281.156	3.887	POS	7-(4-Hydroxyphenyl)-1-phenyl-4-hepten-3-one	[M+H]+	0.00270	2.86	6.1E-09	9.76
455.102	0.673	NEG	3,5,7-Tris(acetyloxy)-8-methoxy-2-(4-methoxyphenyl)-4H-1-benzopyran-4-one	[M-H]-	0.00360	3.91	6.5E-09	0.06
526.252	4.595	NEG	N-[(3a,5b,7a,12a)-3,12-dihydroxy-24-oxo-7-(sulfoxy)cholan-24-yl]-Glycine	$[M-H_2O-H]-$	0.00250	5.41	6.7E-09	2.26
439.087	0.722	NEG	3,5-Dihydroxyphenyl 1-O-(6-O-galloyl-beta-D-glucopyranoside)	[M-H]-	-0.00160	10.76	1.2E-08	0.07
231.023	0.716	NEG	6,7-Benzocoumarin	[M+Cl]-	0.00200	3.35	3.7E-08	18.75
338.989	0.814	NEG	alpha-D-Glucose 1,6-biphosphate	[M-H]-	0.00030	2.16	4.0E-08	0.25
367.103	0.714	NEG	5-O-Feruloylquinic acid	[M-H]-	-0.00010	2.92	7.4E-08	46.68
263.197	0.735	POS	2-Methylbutyroylcarnitine	$[M+NH_4]+$	0.00180	2.75	8.9E-08	1.74
132.030	0.693	NEG	L-Aspartic Acid	[M-H]-	-0.00040	4.75	9.3E-08	2.54
191.020	0.932	NEG	Citric acid	[M-H]-	0.00040	7.26	1.0E-07	0.27
414.199	1.214	POS	1-(3-Methylbutanoyl)-6-apiosylglucose	$[M+NH_4]+$	0.00330	2.41	2.4E-07	0.61
565.048	0.824	NEG	UDP-glucose	[M-H]-	0.00040	9.68	4.7E-07	4.71
426.022	0.970	NEG	Deoxyguanosine diphosphate (dGDP)	[M-H]-	0.00010	3.54	6.4E-07	0.41
516.231	1.416	POS	Alpha-Trisaccharide	[M+H]+	0.00190	3.32	9.5E-07	0.54
476.048	0.757	NEG	CDP-glycerol	[M-H]-	0.00070	3.06	1.1E-06	5.12
474.146	0.701	NEG	Trp-Leu-OH	[M+Cl]-	0.00340	2.93	1.8E-06	0.09
164.071	2.131	NEG	L-Phenylalanine	[M-H]-	-0.00030	2.77	2.7E-06	1.72
587.159	0.715	NEG	Aurasperone E	[M-H]-	0.00340	3.25	3.1E-06	0.27
264.934	0.634	NEG	Tris(2-chloroethyl)phosphate	$[M-H_2O-H]-$	-0.00300	2.27	5.4E-05	2.01
606.075	0.830	NEG	Uridine diphosphate-N-acetylglucosamine	[M-H]-	0.00030	5.61	7.8E-05	1.59
323.029	0.884	NEG	Uridine monophosphate (UMP)	[M-H]-	0.00050	3.17	1.0E-04	1.96
120.081	2.146	POS	Tyramine	$[M+H-H_2O]+$	-0.00090	3.15	1.2E-04	1.52
117.019	1.304	NEG	Succinic acid	[M-H]-	0.00010	2.92	1.6E-04	1.64
146.118	0.755	POS	2-amino-heptanoic acid	[M+H]+	0.00000	7.36	3.1E-04	1.54
162.078	0.891	POS	D-Galactosamine	$[M+H-H_2O]+$	0.00060	2.45	8.2E-04	2.04
131.071	5.132	NEG	D-Leucic acid	[M-H]-	-0.00010	3.54	1.2E-03	0.65
497.076	12.732	NEG	dTDP-L-rhodinose	$[M-H_2O-H]-$	0.00170	6.50	1.3E-03	2.71
415.212	9.792	POS	Estra-1,3,5(10)-triene-3,6alpha,17beta-triol triacetate	[M+H]+	0.00050	8.04	1.8E-03	0.62
851.399	9.792	POS	Digitoxigenin 3-[glucosyl-(1->6)-glucosyl-(1->4)-2,6-dideoxyribohexoside]	[M+Na]+	-0.00490	3.22	2.2E-03	0.63
288.290	8.542	POS	Margaric acid	$[M+NH_4]+$	0.00220	3.20	4.2E-03	0.58
531.409	12.551	POS	VITAMIN E SUCCINATE	[M+H]+	0.00470	6.26	4.4E-03	1.55
298.097	4.125	POS	(methylthio)adenosine	[M+H]+	0.00030	2.35	5.4E-03	1.57
449.173	9.782	NEG	Bis(3-azidopyridinium)-1,10-decane perchlorate	[M-H]-	-0.00090	2.69	5.4E-03	0.62
356.280	14.888	POS	5,6-dihydroxy-8,11,14-eicosatrienoic acid	$[M+NH_4]+$	0.00200	3.03	6.0E-03	2.02
459.202	9.782	NEG	Formestane-4-O-glucuronide	$[M-H_2O-H]-$	-0.00130	5.62	6.3E-03	0.65
423.057	11.567	NEG	Asp-Phe-OH	[M+Cl]-	-0.00210	2.63	9.4E-03	1.78
362.051	0.898	NEG	Guanidylic acid (guanosine monophosphate)	[M-H]-	0.00060	2.31	9.9E-03	1.89

[a]M/Z, mass/charge number of each peak in mass spectra. [b]R.T.(min), retention time of each metabolite in chromatography. [c]The formation of each peak in mass spectra. [d]△m, the mass discrepancies between measured values and theoretical values during metabolite identification in database HMDB and METLIN. [e] Differences of metabolite abundances between CCFM8610 and CCFM191 were analyzed using one-way analysis of variance (ANOVA), followed by the Tukey post hoc test. $P < 0.05$ is considered as significant. [f]The abundance difference of each metabolite is expressed as the ratio of the average content in CCFM8610 and in CCFM191 (CCFM8610/CCFM191) (n=6). A value >1 represents that the corresponding metabolite is in higher abundance in CCFM8610, while a

value <1 indicates that the corresponding metabolite is in lower abundance in CCFM8610.

Table S2 Changed metabolites in *Lactobacillus plantarum* CCFM8610 after Cd exposure

M/Z[a]	**R.T. (min)[b]**	**Ion mode**	**Metabolites**	**Adduct[c]**	**Δ m[d]**	**VIP**	***P* value[e]**	**Fold change[f]**
377.086	0.698	NEG	D-Lactose	[M+Cl]-	0.00080	24.27	2.2E-14	21.81
179.056	0.714	NEG	D-Fructose	[M-H]-	-0.00010	9.35	3.3E-13	0.15
583.273	4.471	NEG	5beta-scymnol sulfate	[M+Cl]-	0.00240	3.11	3.7E-13	0.27
245.114	3.460	NEG	Aspartyl-Isoleucine	[M-H]-	-0.00050	2.08	1.0E-12	0.42
624.336	4.494	NEG	Glycochenodeoxycholic acid 3-glucuronide	[M-H]-	-0.00300	6.27	2.7E-12	0.18
263.197	0.735	POS	2-Methylbutyroylcarnitine	$[M+NH_4]+$	0.00180	3.65	6.5E-12	0.24
439.087	0.722	NEG	3,5-Dihydroxyphenyl 1-O-(6-O-galloyl-beta-D-glucopyranoside)	[M-H]-	-0.00160	11.92	1.4E-10	18.36
268.085	0.691	NEG	Acetyl-L-tyrosine	[M+FA-H]-	-0.00530	2.01	2.0E-10	0.23
526.252	4.595	NEG	N-[(3a,5b,7a,12a)-3,12-dihydroxy-24-oxo-7-(sulfoxy)cholan-24-yl]-Glycine	$[M-H_2O-H]-$	0.00250	6.08	3.2E-10	0.28
463.183	4.167	NEG	2-[4-(3-Hydroxypropyl)-2-methoxyphenoxy]-1,3-propanediol 1-glucoside	[M+FA-H]-	-0.00590	6.08	1.0E-09	0.54
541.226	1.568	NEG	Cinncassiol 19-glucoside	[M-H]-	-0.00320	2.24	1.2E-09	0.49
455.102	0.673	NEG	3,5,7-Tris(acetyloxy)-8-methoxy-2-(4-methoxyphenyl)-4H-1-benzopyran-4-one	[M-H]-	0.00360	3.94	1.5E-09	17.27
446.187	0.735	POS	b-D-Xylopyranosyl-(1->4)-a-L-rhamnopyranosyl-(1->2)-L-arabinose	$[M+NH_4]+$	0.00230	2.58	2.7E-09	15.03
360.150	0.810	POS	Sucrose	$[M+NH_4]+$	0.00190	2.10	3.7E-09	25.35
128.036	0.958	NEG	L-Glutamate	$[M-H_2O-H]-$	-0.00070	6.63	4.0E-09	0.59
514.215	1.413	NEG	Alpha-Trisaccharide	[M-H]-	0.00120	3.16	4.5E-09	0.58
521.172	0.708	NEG	O-Desmethylquinidine glucuronide	[M+Cl]-	0.00350	2.27	5.9E-09	6.34
152.036	1.063	POS	2-Methoxy-4-nitrophenol	$[M+H-H_2O]+$	0.00070	2.44	9.4E-09	5.39
203.065	0.725	NEG	L-beta-aspartyl-L-alanine	[M-H]-	-0.00190	2.16	1.5E-08	0.30
593.195	0.743	NEG	punaglandin	[M+Cl]-	0.00310	2.48	2.6E-08	15.63
132.030	0.693	NEG	L-Aspartic Acid	[M-H]-	-0.00040	4.82	5.8E-08	0.36
168.991	0.765	NEG	D-Glyceraldehyde 3-phosphate	[M-H]-	0.00040	4.24	6.3E-08	0.50
281.156	3.887	POS	7-(4-Hydroxyphenyl)-1-phenyl-4-hepten-3-one	[M+H]+	0.00270	2.53	7.1E-08	0.28
231.023	0.716	NEG	6,7-Benzocoumarin	[M+Cl]-	0.00200	3.19	8.7E-08	0.12
118.051	0.684	NEG	L-Threonine	[M-H]-	-0.00030	2.04	8.9E-08	0.42
367.103	0.714	NEG	5-O-Feruloylquinic acid	[M-H]-	-0.00010	2.84	9.0E-08	0.04
241.118	5.030	NEG	L-gamma-glutamyl-L-isoleucine	$[M-H_2O-H]-$	-0.00210	2.58	9.3E-08	0.45
226.012	0.832	NEG	L-Glutamyl 5-phosphate	[M-H]-	-0.00010	2.25	1.1E-07	0.30
431.109	0.740	NEG	TyrMe-Asp-OH	[M-H]-	-0.00070	2.16	1.2E-07	5.71
147.066	1.221	NEG	Mevalonic acid	[M-H]-	-0.00040	2.14	3.3E-07	5.68
465.199	4.177	POS	Acarbose	$[M+H-H_2O]+$	0.00100	4.53	3.9E-07	0.64
513.025	0.706	NEG	Fucofuroeckol B	[M+Cl]-	0.00250	3.17	5.0E-07	12.66
387.116	0.670	NEG	Fructoselysine 6-phosphate	[M-H]-	-0.00180	4.20	7.8E-07	7.65
260.090	0.741	NEG	Aspartyl-Glutamine	[M-H]-	0.00110	2.26	9.4E-07	0.41
381.079	0.691	POS	Dihydrocaffeic acid 3-O-glucuronide	[M+Na]+	0.00010	4.84	1.6E-06	14.84
117.056	3.506	NEG	3-hydroxy valeric acid	[M-H]-	-0.00010	2.75	1.6E-06	2.54
606.075	0.830	NEG	Uridine diphosphate-N-acetylglucosamine	[M-H]-	0.00030	6.91	3.4E-06	0.44
587.159	0.715	NEG	Aurasperone E	[M-H]-	0.00340	4.63	4.1E-06	6.74
565.048	0.824	NEG	UDP-glucose	[M-H]-	0.00040	8.34	8.2E-06	0.40
476.048	0.757	NEG	CDP-glycerol	[M-H]-	0.00070	2.76	8.6E-06	0.33
131.071	5.132	NEG	D-Leucic acid	[M-H]-	-0.00010	4.96	8.6E-06	2.03
474.146	0.701	NEG	Trp-Leu-OH	[M+Cl]-	0.00340	2.83	8.9E-06	11.23
160.062	0.964	NEG	4-Methyl-L-glutamate	[M-H]-	0.00020	2.75	1.1E-05	1.84
251.078	0.891	NEG	Deoxyinosine	[M-H]-	-0.00090	3.37	2.0E-05	1.63
470.261	4.076	POS	Sphingofungin A	[M+K]+	-0.00160	2.05	3.0E-05	0.37
146.118	0.755	POS	2-amino-heptanoic acid	[M+H]+	0.00000	8.59	3.9E-05	0.53
323.029	0.884	NEG	Uridine monophosphate (UMP)	[M-H]-	0.00050	2.59	8.6E-04	0.63
302.246	12.918	POS	All-Trans-3,4-Didehydro Retinol	$[M+NH_4]+$	-0.00050	2.76	6.1E-03	0.37

[a]M/Z, mass/charge number of each peak in mass spectra. [b]R.T.(min), retention time of each metabolite in chromatography. [c]The formation of each peak in mass spectra. [d]△m, the mass discrepancies between measured values and theoretical values during metabolite identification in database HMDB and METLIN. [e] Differences between the control and the Cd-treated were analyzed using one-way analysis of variance (ANOVA), followed by the Tukey post hoc test. $P < 0.05$ is considered as significant. [f]The change of metabolite abundance is expressed as the ratio of the average content in Cd exposed group and in control (CCFM8610 (Cd)/CCFM8610(0)) (n=6). A

value >1 represents upregulation, while a value <1 indicates downregulation.

Table S3 Changed metabolites in *Lactobacillus plantarum* CCFM191 after Cd exposure

M/Z[a]	R.T. (min)[b]	Ion mode	Metabolites	Adduct[c]	Δ m[d]	VIP	*P* value[e]	Fold change[f]
168.991	0.765	NEG	D-Glyceraldehyde 3-phosphate	[M-H]-	0.00040	7.74	2.0E-14	0.05
429.199	3.412	NEG	Ptilosteroid B	[M-H]-	0.00380	12.35	1.7E-11	2.32
463.183	4.167	NEG	2-[4-(3-Hydroxypropyl)-2-methoxyphenoxy]-1,3-propanediol 1-glucoside	[M+FA-H]-	-0.00590	7.47	1.5E-09	1.56
117.056	3.506	NEG	3-hydroxy valeric acid	[M-H]-	-0.00010	5.30	4.2E-09	3.28
606.075	0.830	NEG	Uridine diphosphate-N-acetylglucosamine	[M-H]-	0.00030	9.28	5.1E-09	0.15
447.156	2.235	NEG	HoPhe-HoPhe-OH	[M-H]-	-0.00060	2.52	5.3E-09	3.11
190.054	4.175	NEG	N-Acetyl-DL-methionine	[M-H]-	-0.00060	2.97	7.0E-09	1.81
160.062	0.964	NEG	4-Methyl-L-glutamate	[M-H]-	0.00020	6.33	1.5E-08	2.63
147.066	1.221	NEG	Mevalonic acid	[M-H]-	-0.00040	6.22	1.5E-08	16.47
431.214	3.445	POS	Palmitoylglycerone phosphate	[M+Na]+	-0.00260	12.73	2.4E-08	2.52
316.115	0.741	NEG	N4-(b-N-Acetyl-D-glucosaminyl)-L-asparagine	[M-H_2O-H]-	-0.00080	2.26	3.9E-08	1.93
149.028	3.723	NEG	2-Hydroxy-4-(methylthio)butanoic acid	[M-H]-	-0.00020	3.20	5.8E-08	3.15
217.082	1.026	NEG	Glutamylalanine	[M-H]-	-0.00100	2.01	7.3E-08	0.59
251.078	0.891	NEG	Deoxyinosine	[M-H]-	-0.00090	4.48	7.9E-08	1.53
298.097	4.125	POS	(methylthio)adenosine	[M+H]+	0.00030	3.19	8.2E-08	0.56
131.071	5.132	NEG	D-Leucic acid	[M-H]-	-0.00010	8.51	1.4E-07	2.03
449.171	2.276	POS	Desmethylmianserin glucuronide	[M+Na]+	0.00220	2.09	1.9E-07	2.94
271.227	10.986	NEG	4-hydroxy palmitic acid	[M-H]-	-0.00070	2.18	2.5E-07	2.03
241.118	5.030	NEG	L-gamma-glutamyl-L-isoleucine	[M-H_2O-H]-	-0.00210	2.96	6.6E-07	0.57
610.185	14.959	POS	Peonidin 3-rhamnoside 5-glucoside	[M+H]+	-0.00470	9.70	1.1E-06	20.30
389.203	1.891	POS	Doxylamine succinate	[M+H]+	-0.00390	3.34	1.5E-06	1.93
321.049	1.069	NEG	dTMP	[M-H]-	-0.00020	2.09	1.7E-06	2.25
613.184	14.959	POS	12-Dihydrodalbinol O-glucoside	[M+Na]+	-0.00570	3.61	2.5E-06	26.15
116.070	0.724	POS	L-Proline	[M+H]+	-0.00010	3.53	4.4E-06	1.87
465.199	4.177	POS	Acarbose	[M+H-H_2O]+	0.00100	6.92	4.7E-06	1.62
116.036	0.907	NEG	2S-amino-3-oxo-butanoic acid	[M-H]-	0.00070	3.83	6.6E-06	1.92
338.989	0.814	NEG	alpha-D-Glucose 1,6-biphosphate	[M-H]-	0.00030	2.19	9.6E-06	0.55
565.048	0.824	NEG	UDP-glucose	[M-H]-	0.00040	4.43	9.9E-06	0.54
446.187	0.735	POS	b-D-Xylopyranosyl-(1->4)-a-L-rhamnopyranosyl-(1->2)-L-arabinose	[M+NH_4]+	0.00230	2.18	3.1E-05	0.58
302.171	1.911	POS	N-[(4-Hydroxy-3-methoxyphenyl)methyl]octanamide	[M+Na]+	-0.00150	2.22	5.2E-05	1.72
299.259	12.254	NEG	DL-2-hydroxy stearic acid	[M-H]-	-0.00060	4.50	6.7E-05	0.60
349.054	0.757	NEG	Pentahydroxyflavanone	[M+FA-H]-	-0.01000	2.29	1.8E-04	2.20
130.050	0.831	POS	4-Oxoproline	[M+H]+	0.00020	2.57	8.5E-04	0.61
413.267	12.362	POS	cholan-24-oic acid	[M+Na]+	0.00040	2.53	5.6E-03	1.86
265.180	14.886	POS	5-Hydroxy-1-(4-hydroxyphenyl)-3-decanone	[M+H]+	0.00030	2.01	6.5E-03	1.80
356.280	14.888	POS	5,6-dihydroxy-8,11,14-eicosatrienoic acid	[M+NH_4]+	0.00200	3.73	6.5E-03	1.78

[a]M/Z, mass/charge number of each peak in mass spectra. [b]R.T.(min), retention time of each metabolite in chromatography. [c]The formation of each peak in mass spectra. [d]△m, the mass discrepancies between measured values and theoretical values during metabolite identification in database HMDB and METLIN. [e] Differences between the control and the Cd-treated were analyzed using one-way analysis of variance (ANOVA), followed by the Tukey post hoc test. $P < 0.05$ is considered as significant. [f]The change of metabolite abundance is expressed as the ratio of the average content in Cd exposed group and in control (CCFM191 (Cd)/CCFM191(0)) (n=6). A value >1 represents upregulation, while a value <1 indicates downregulation.

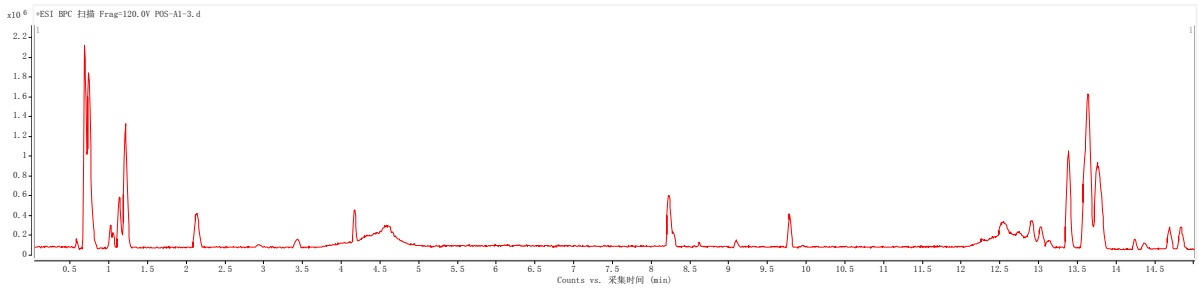

Figure S1 The representative base peak intensity (BPI) chromatogram of CCFM8610 without Cd in positive ion mode.

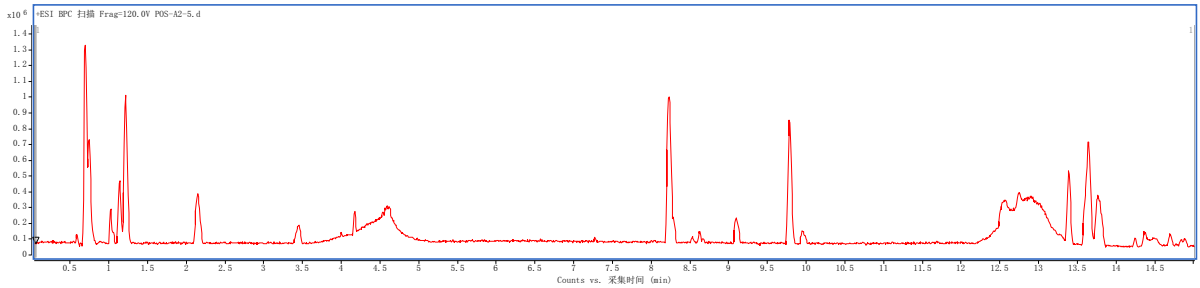

Figure S2 The representative BPI chromatogram of CCFM8610 with Cd in positive ion mode.

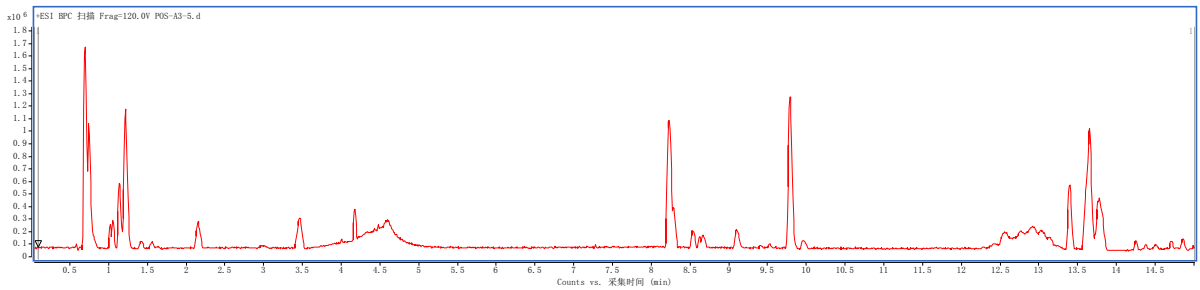

Figure S3 The representative BPI chromatogram of CCFM191 without Cd in positive ion mode.

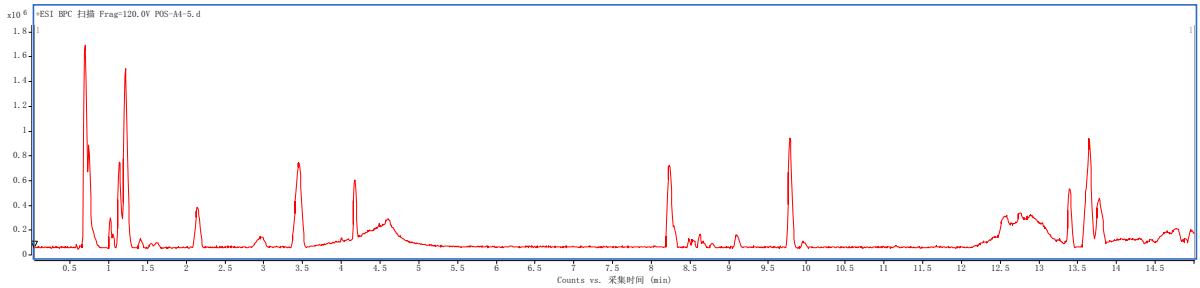

Figure S4 The representative BPI chromatogram of CCFM191 with Cd in positive ion mode.

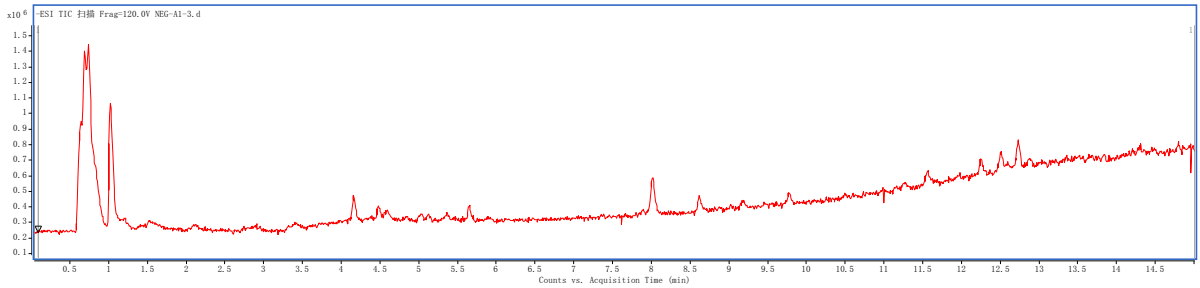

Figure S5 The representative BPI chromatogram of CCFM8610 without Cd in negative ion mode.

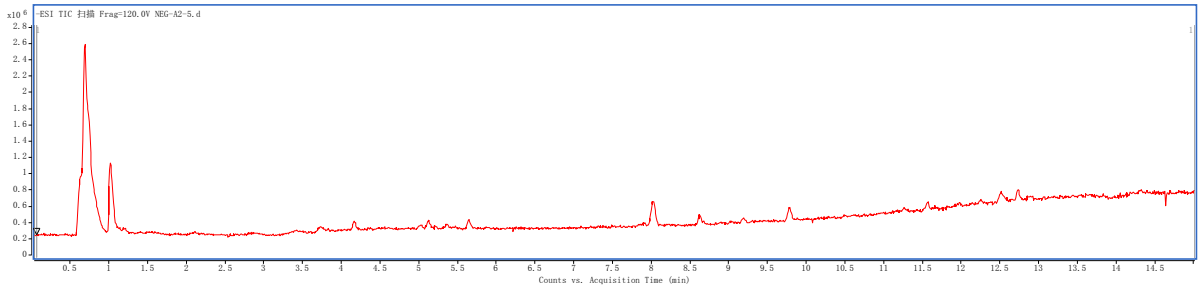

Figure S6 The representative BPI chromatogram of CCFM8610 with Cd in negative ion mode.

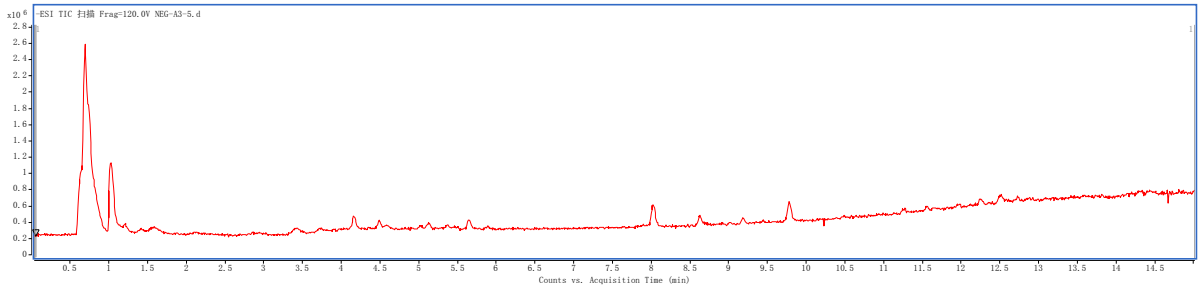

Figure S7 The representative BPI chromatogram of CCFM191 without Cd in negative ion mode.

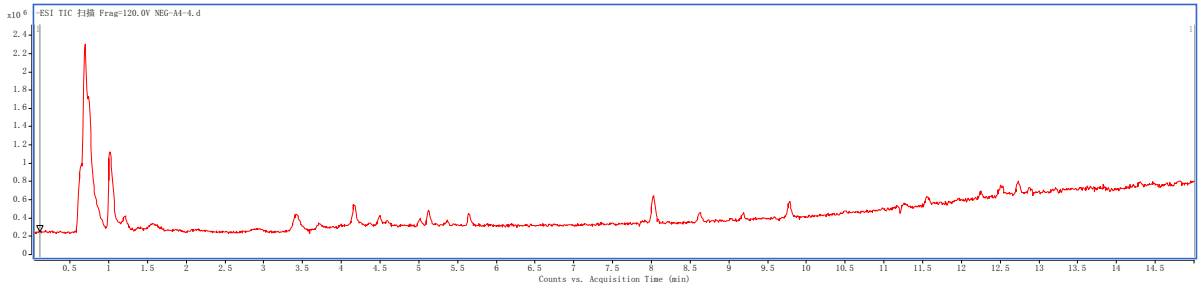

Figure S8 The representative BPI chromatogram of CCFM191 with Cd in negative ion mode.

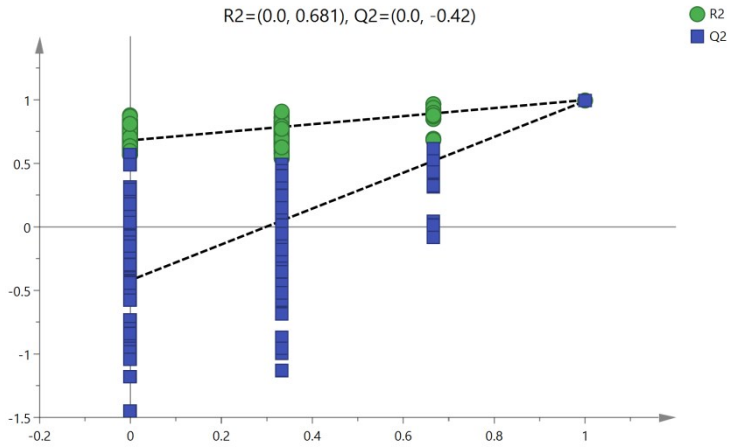

Figure S9 Cross-validation of the pair-wise orthogonal partial least-squares discriminant analysis (OPLS-DA) model of CCFM8610/CCFM191.

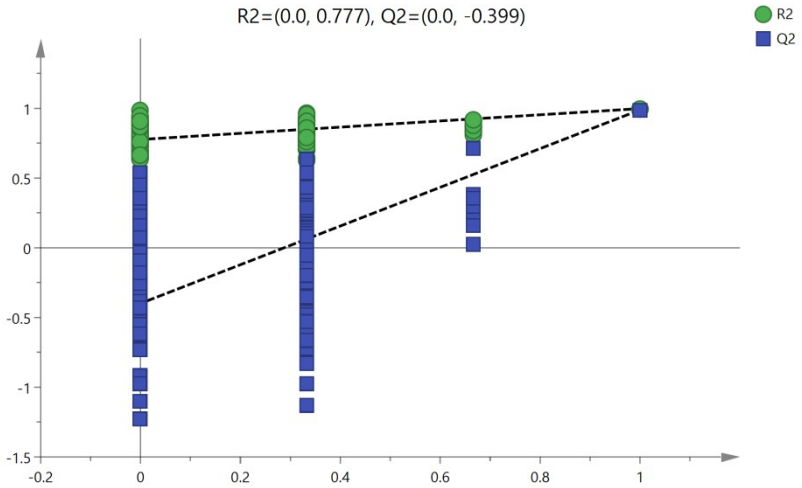

Figure S10 Cross-validation of the OPLS-DA model of CCFM8610(Cd)/8610(0).

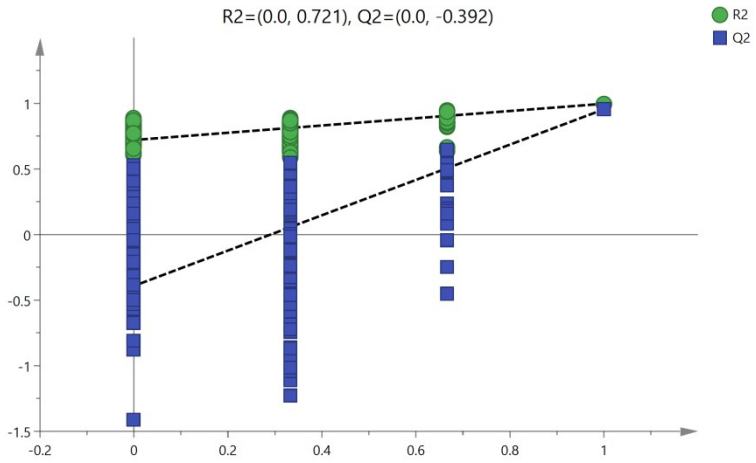

Figure S11 Cross-validation of the OPLS-DA model of CCFM191(Cd)/CCFM191(0).