Supplementary materials

Systemic metabolomics characterization of the ascending and descending property

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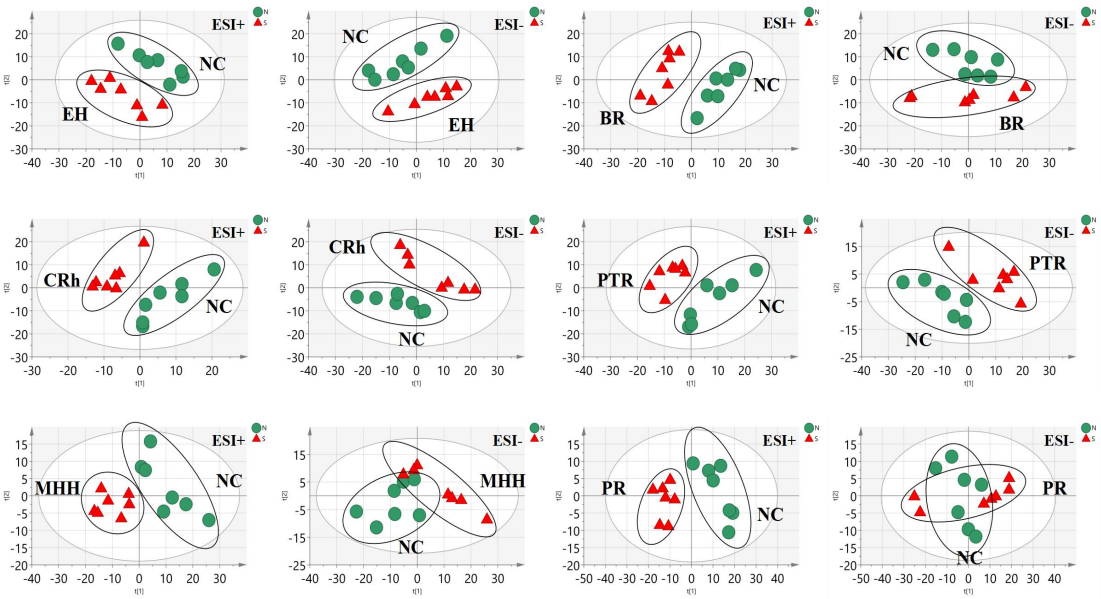
Weisheng Feng (fwsh@hactcm.edu.cn).



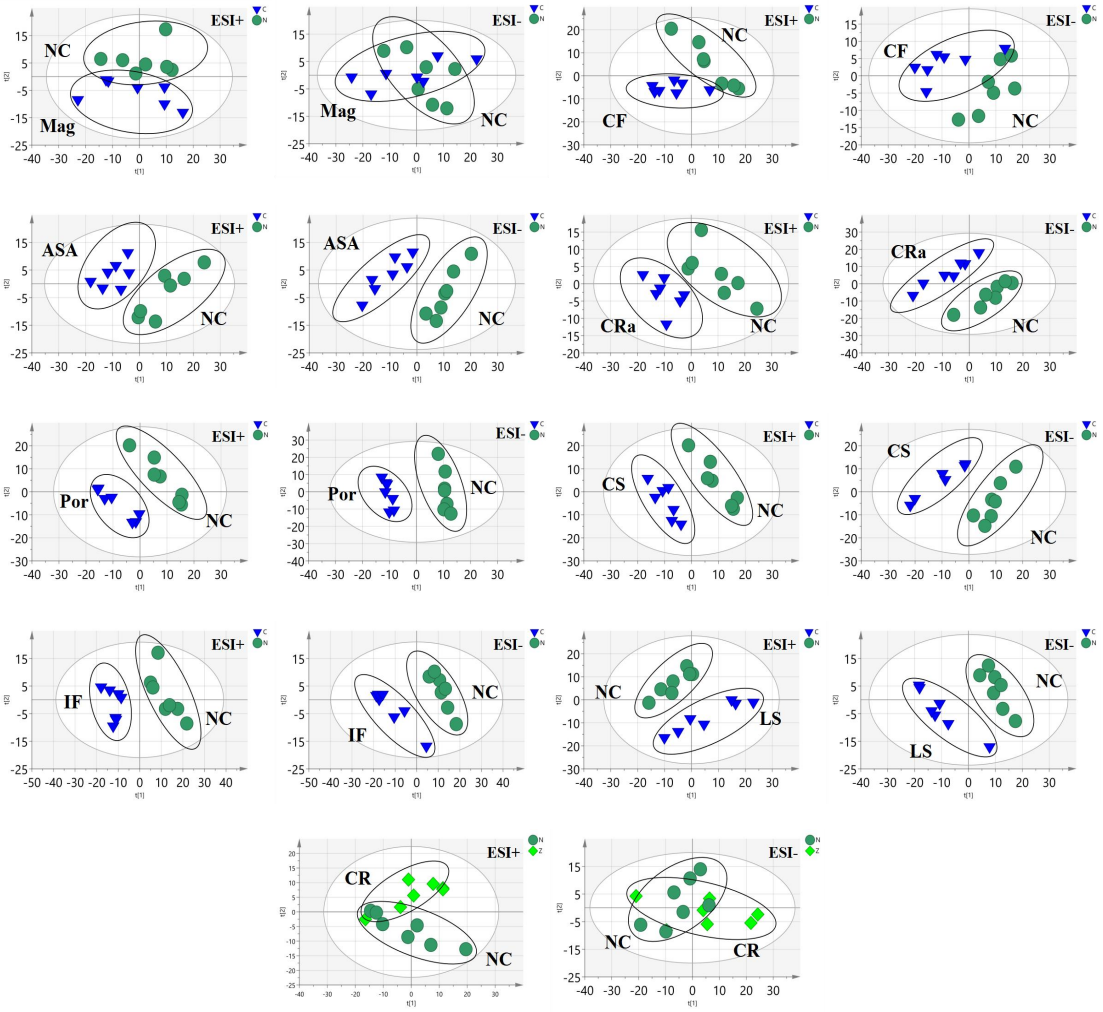
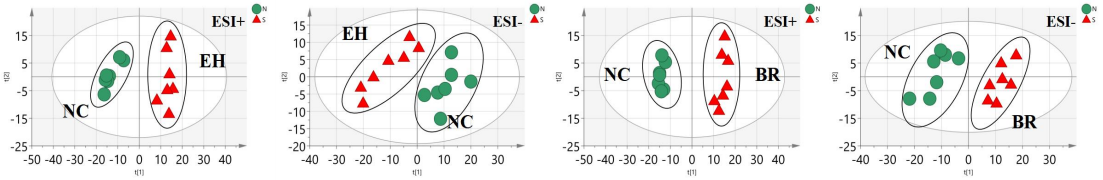


Fig. S1 PCA score scatter plots obtained from heart sample

(EH: *Ephedrae Herba*; BR: *Bupleuri Radix*; CRh: *Cimicifugae Rhizoma*; PTR: *Puerariae Thomsonii Radix*; MHH: *Menthae Haplocalycis Herba*; PR: *Platycodonis Radix*; Mag: *Magnetitum*; CF: *Caryophylli Flos*; ASA: *Armeniacae Semen Amarum*; CRa: *Cyathulae Radix*; Por: *Poria*; CS: *Canavaliae Semen*; IF: *Inulae Flos*; LS: *Lepidii Semen*; CR: *Chuanxiong Rhizoma*)



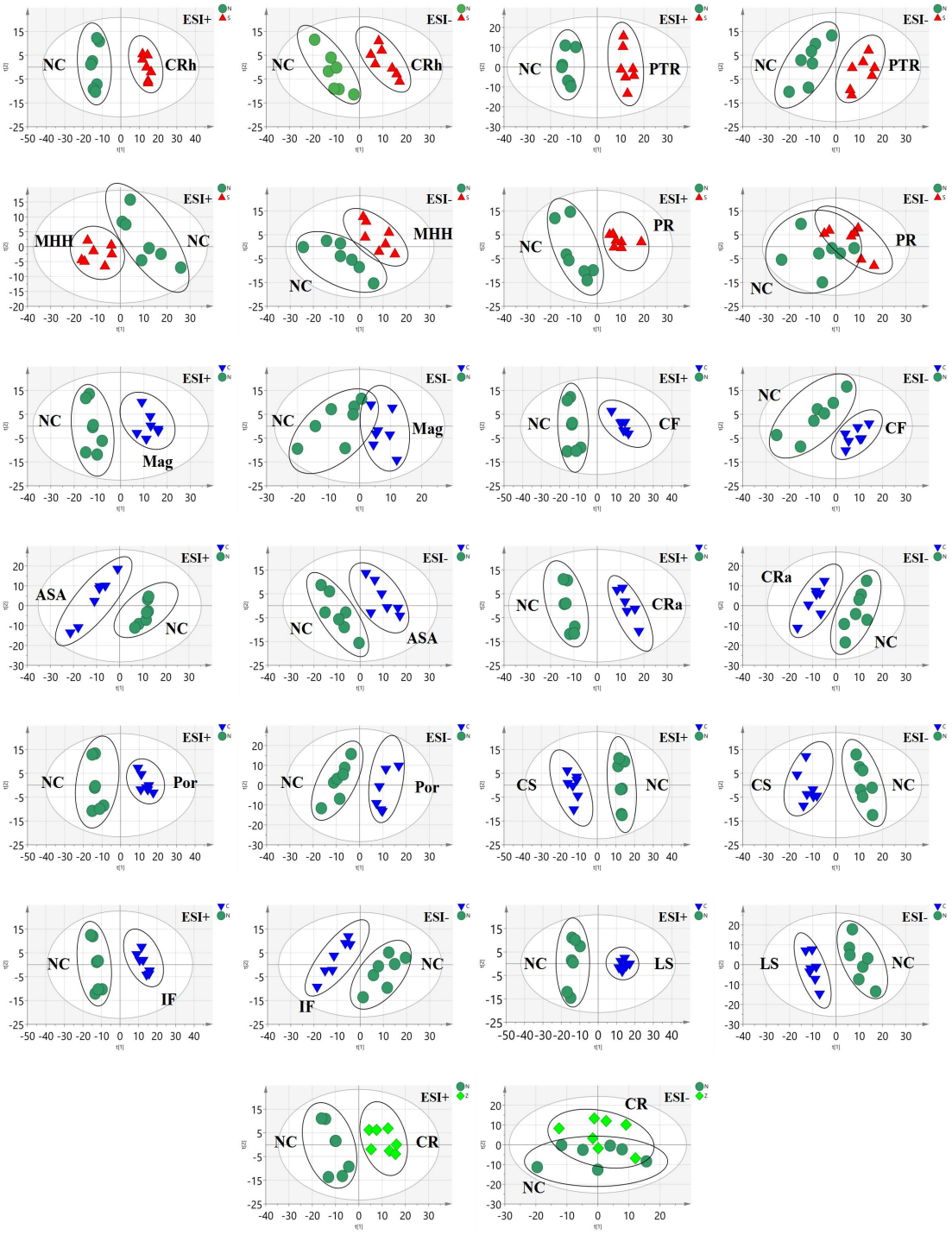


Fig. S 2 PCA score scatter plots obtained from liver sample

(EH: *Ephedrae Herba*; BR: *Bupleuri Radix*; CRh: *Cimicifugae Rhizoma*; PTR: *Puerariae Thomsonii Radix*; MHH: *Menthae Haplocalycis Herba*; PR: *Platycodonis Radix*; Mag: *Magnetitum*; CF: *Caryophylli Flos*; ASA: *Armeniacae Semen Amarum*; CRa: *Cyathulae Radix*; Por: *Poria*; CS: *Canavaliae Semen*; IF: *Inulae Flos*; LS: *Lepidii Semen*; CR: *Chuanxiong Rhizoma*)

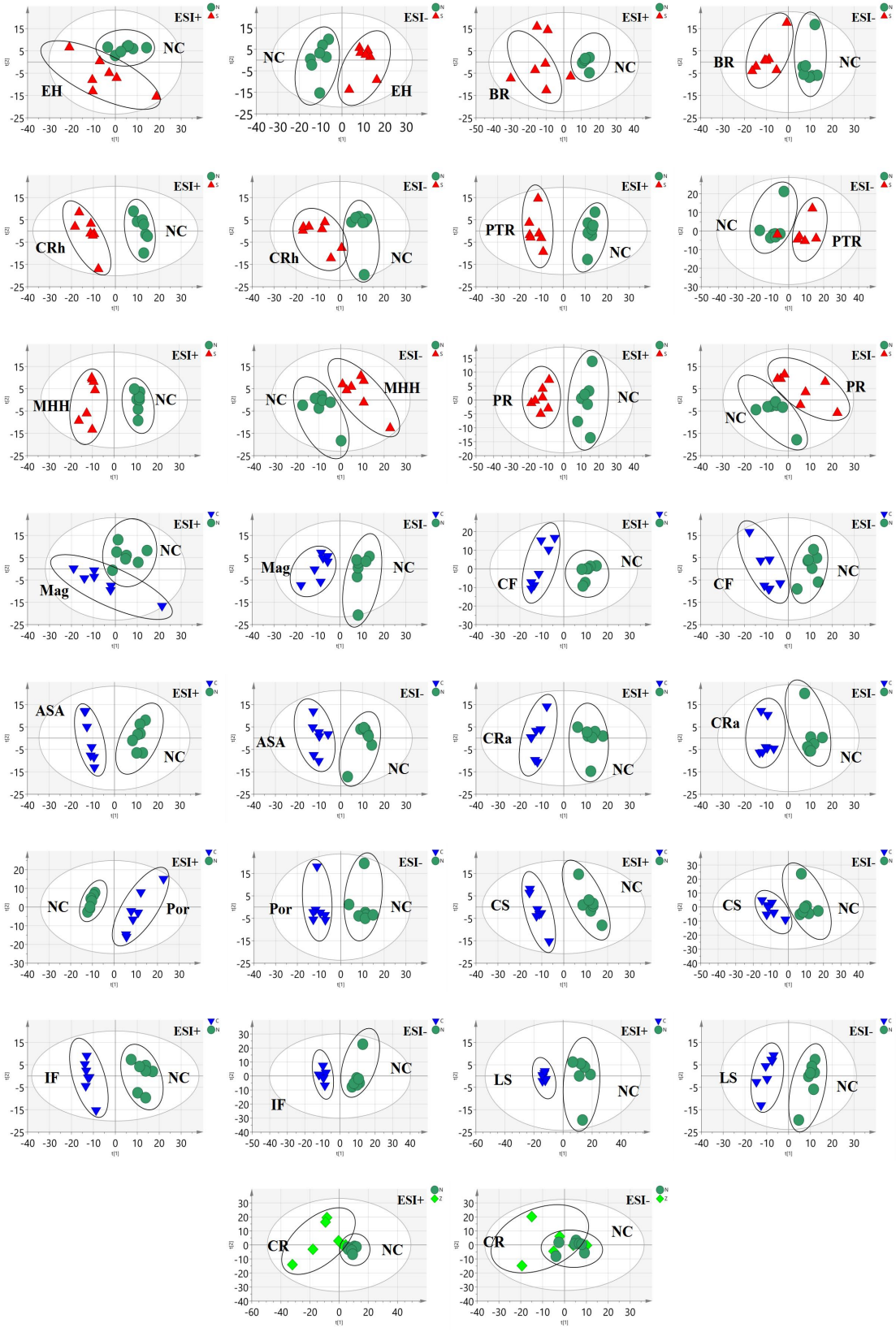
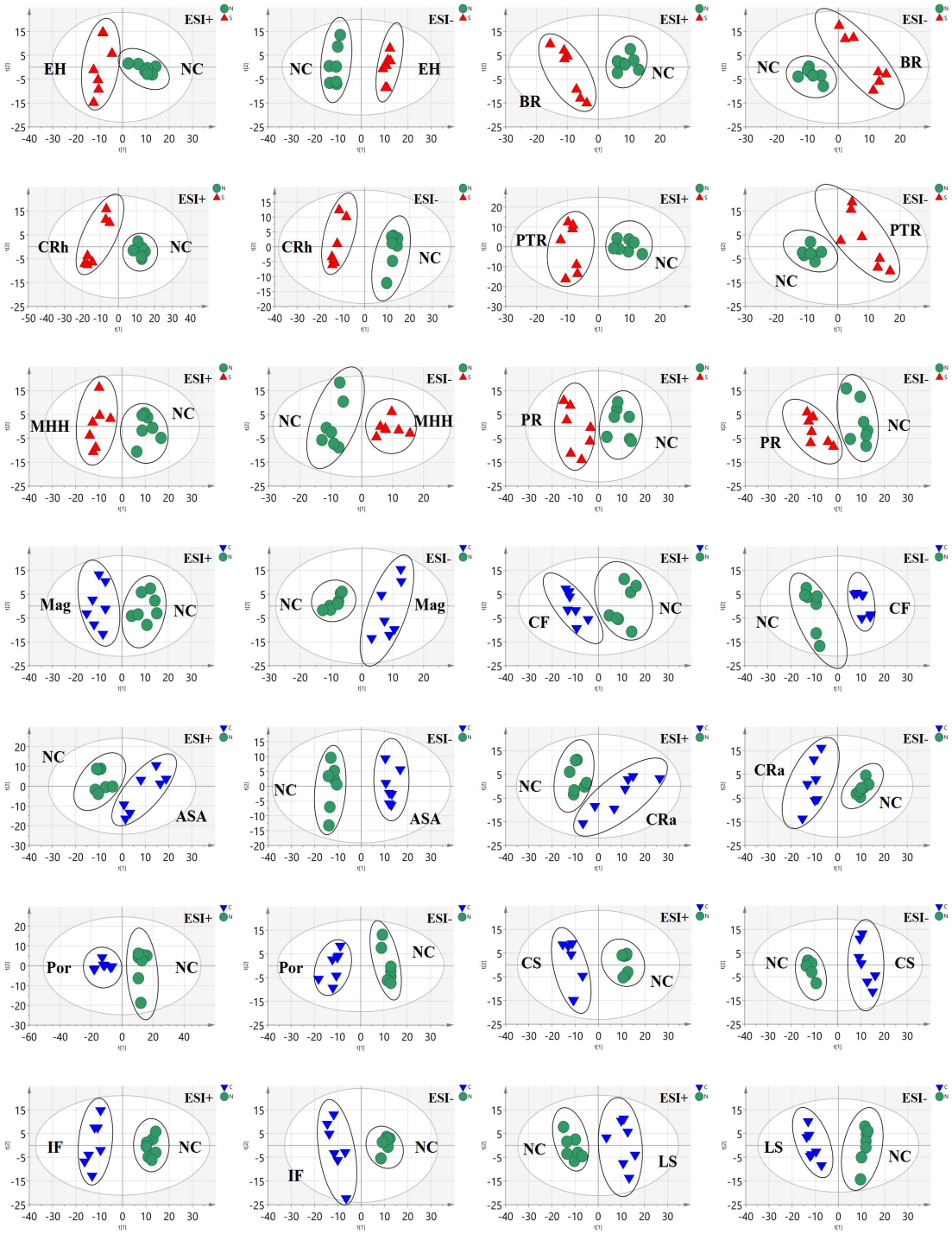


Fig. S 3 PCA score scatter plots obtained from lung sample

(EH: *Ephedrae Herba*; BR: *Bupleuri Radix*; CRh: *Cimicifugae Rhizoma*; PTR:

Puerariae Thomsonii Radix; MHH: *Menthae Haplocalycis Herba*; PR: *Platycodonis Radix*; Mag: *Magnetitum*; CF: *Caryophylli Flos*; ASA: *Armeniacae Semen Amarum*; CRa: *Cyathulae Radix*; Por: *Poria*; CS: *Canavaliae Semen*; IF: *Inulae Flos*; LS: *Lepidii Semen*; CR: *Chuanxiong Rhizoma*)



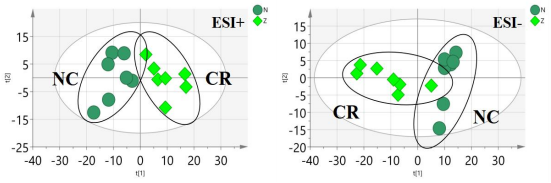
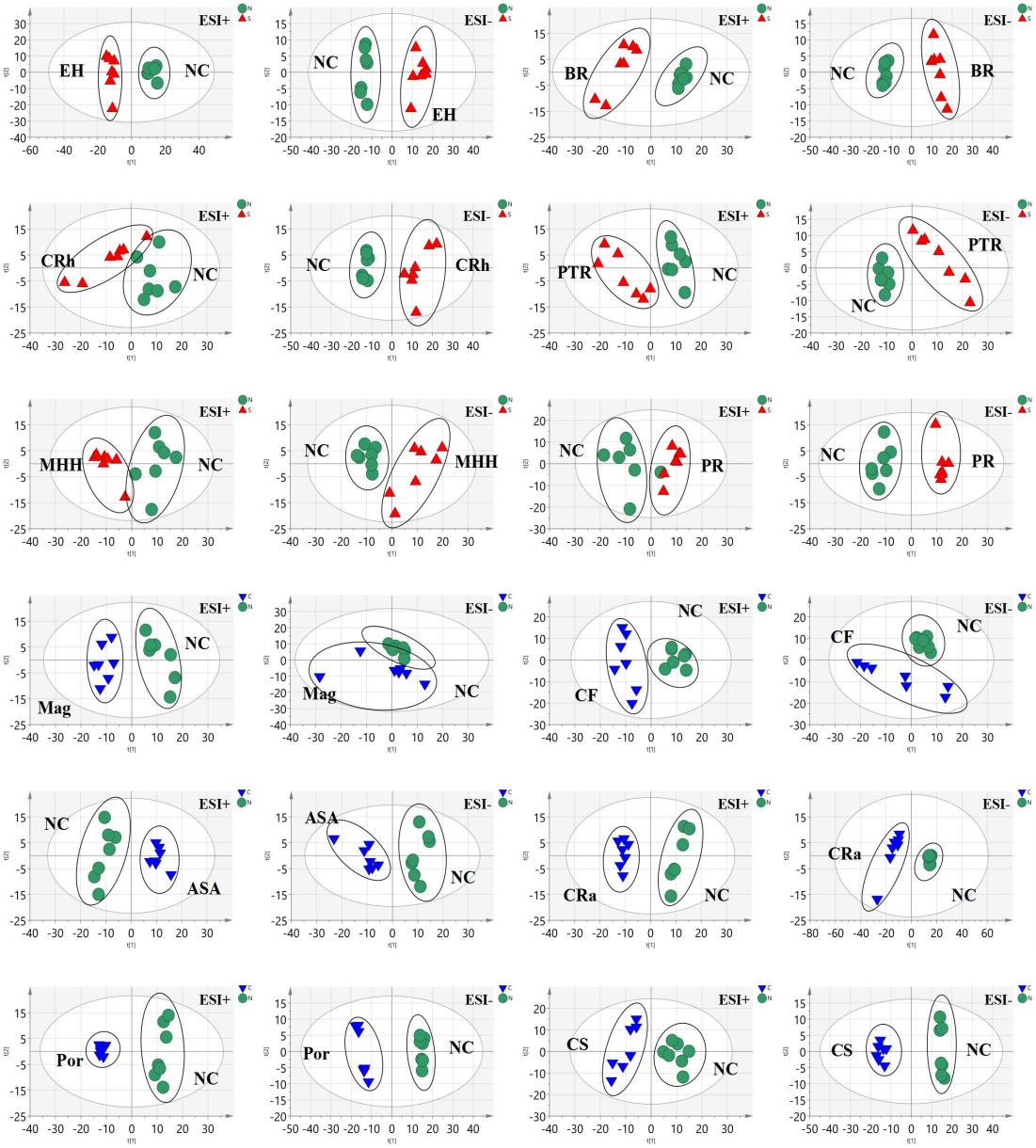


Fig. S 4 PCA score scatter plots obtained from kidney sample

(EH: *Ephedrae Herba*; BR: *Bupleuri Radix*; CRh: *Cimicifugae Rhizoma*; PTR: *Puerariae Thomsonii Radix*; MHH: *Menthae Haplocalycis Herba*; PR: *Platycodonis Radix*; Mag: *Magnetitum*; CF: *Caryophylli Flos*; ASA: *Armeniacae Semen Amarum*; CRa: *Cyathulae Radix*; Por: *Poria*; CS: *Canavaliae Semen*; IF: *Inulae Flos*; LS: *Lepidii Semen*; CR: *Chuanxiong Rhizoma*)



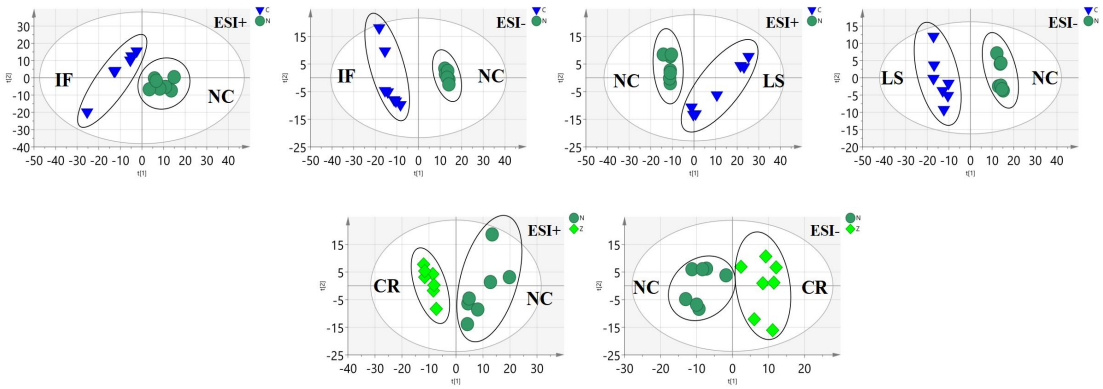
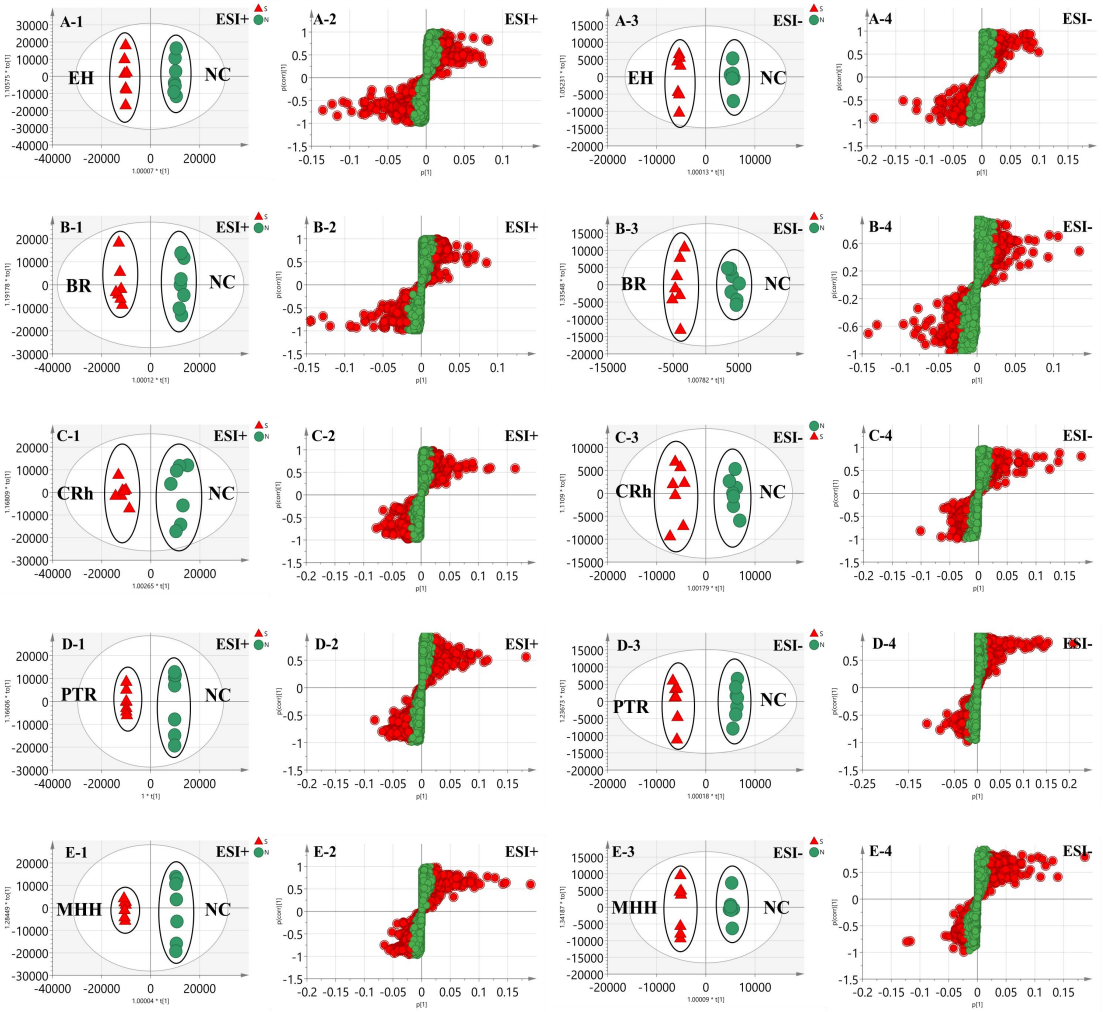
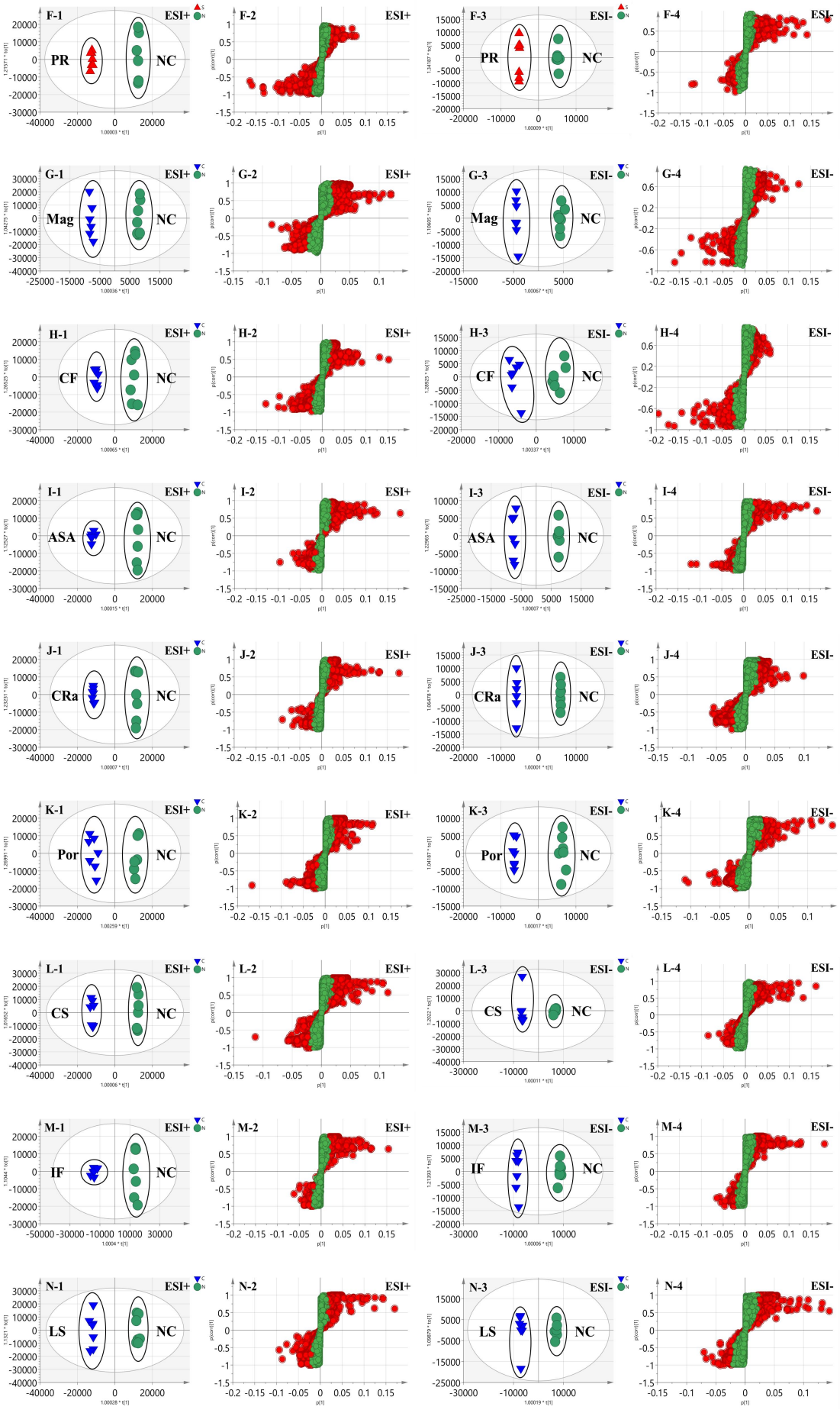


Fig. S 5 PCA score scatter plots obtained from spleen sample

(EH: *Ephedrae Herba*; BR: *Bupleuri Radix*; CRh: *Cimicifugae Rhizoma*; PTR: *Puerariae Thomsonii Radix*; MHH: *Menthae Haplocalycis Herba*; PR: *Platycodonis Radix*; Mag: *Magnetitum*; CF: *Caryophylli Flos*; ASA: *Armeniacae Semen Amarum*; CRa: *Cyathulae Radix*; Por: *Poria*; CS: *Canavaliae Semen*; IF: *Inulae Flos*; LS: *Lepidii Semen*; CR: *Chuanxiong Rhizoma*)

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ESI+
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ESI-
Mag
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G-4
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H-2
ESI+
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I-3
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ESI+
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ESI-
IF
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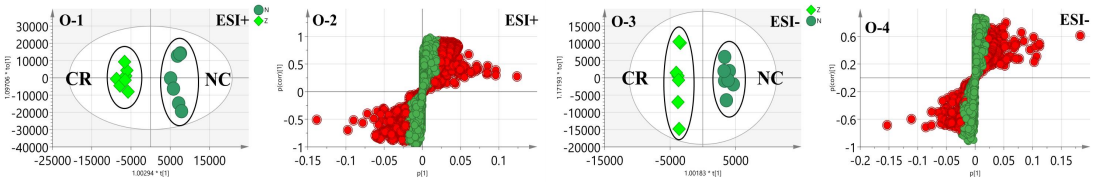
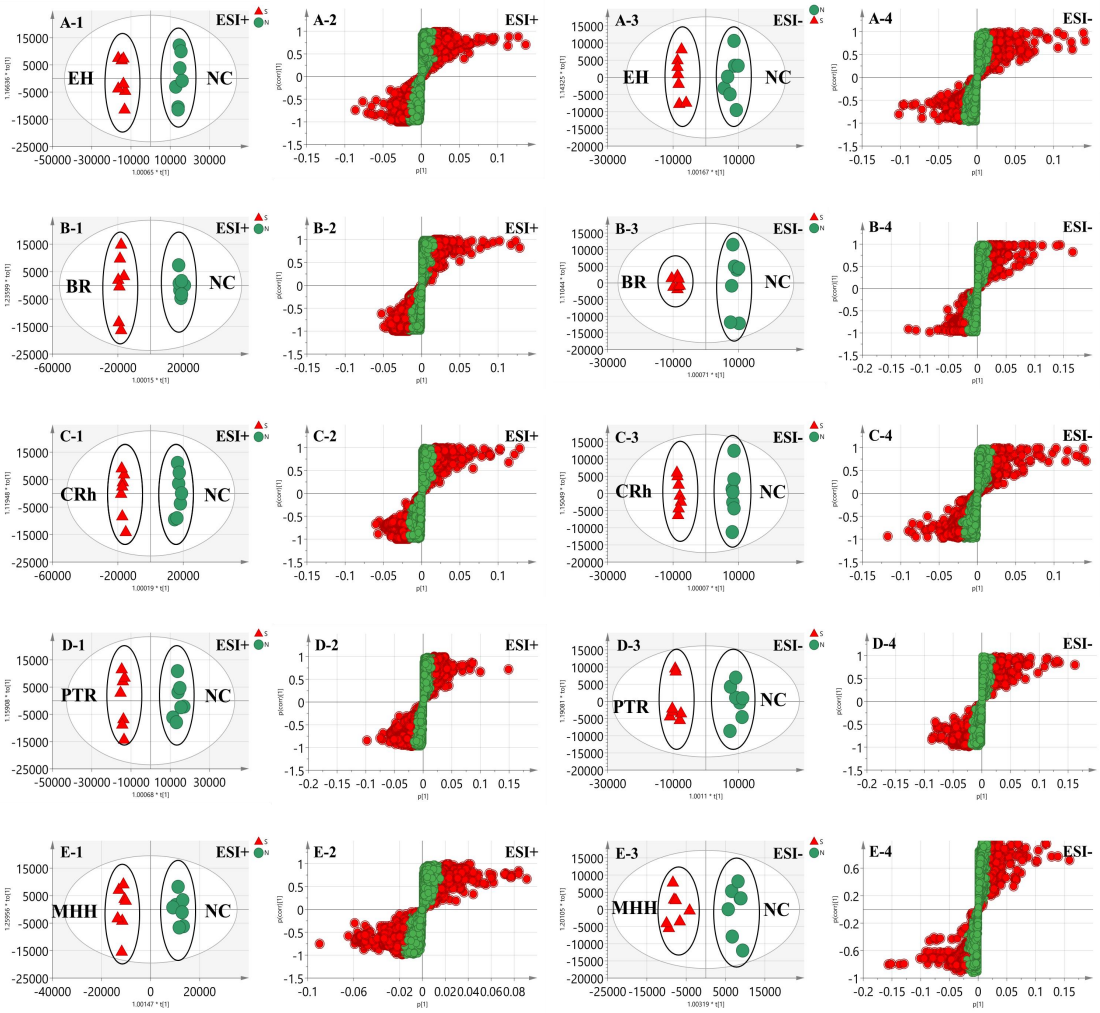
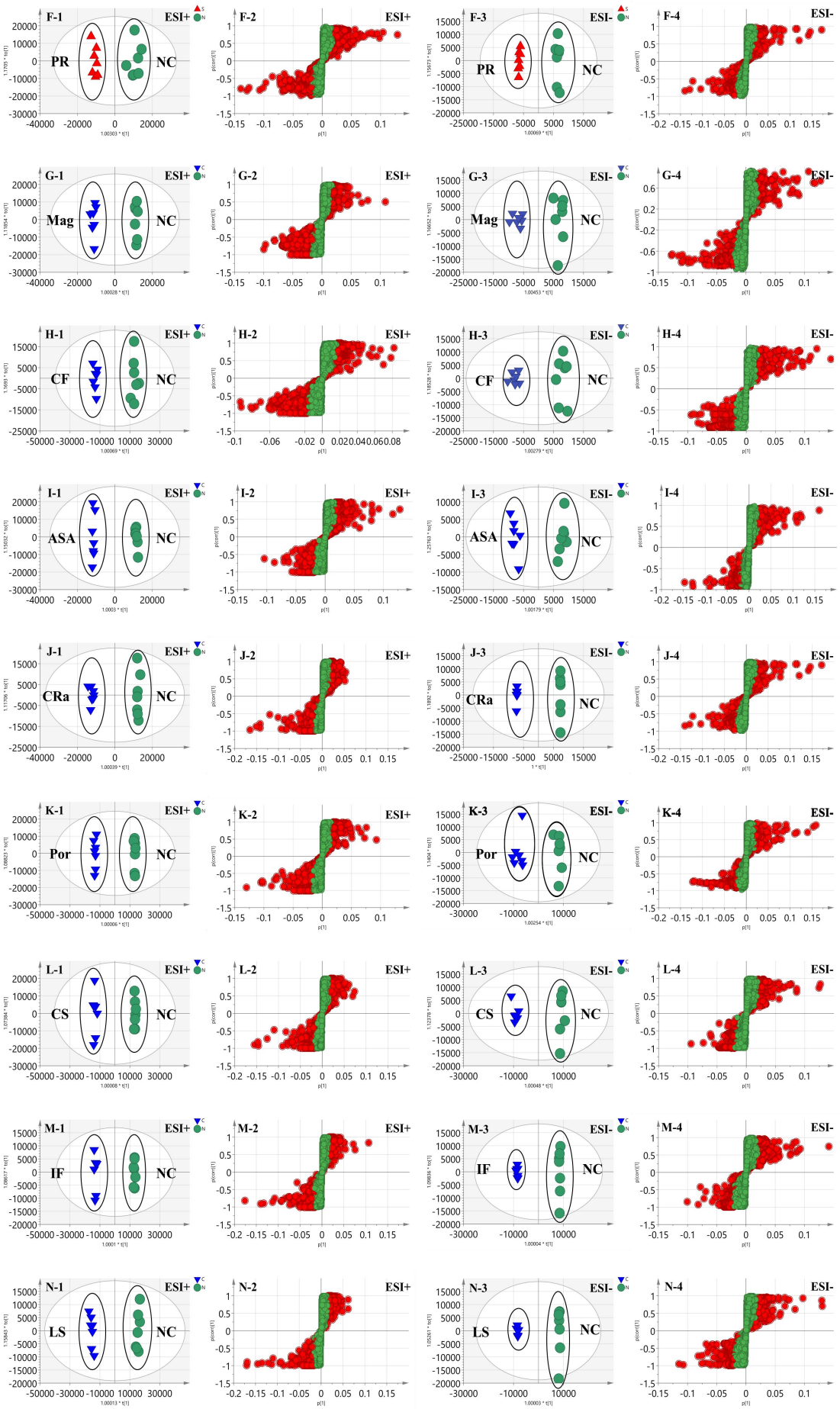


Fig. S 6 OPLS-DA score plots and S-plots in negative ion mode obtained from heart sample

(EH: *Ephedrae Herba*; BR: *Bupleuri Radix*; CRh: *Cimicifugae Rhizoma*; PTR: *Puerariae Thomsonii Radix*; MHH: *Menthae Haplocalycis Herba*; PR: *Platycodonis Radix*; Mag: *Magnetitum*; CF: *Caryophylli Flos*; ASA: *Armeniacae Semen Amarum*; CRa: *Cyathulae Radix*; Por: *Poria*; CS: *Canavaliae Semen*; IF: *Inulae Flos*; LS: *Lepidii Semen*; CR: *Chuanxiong Rhizoma*)

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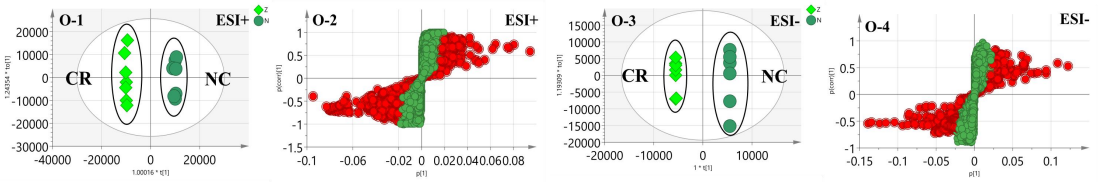
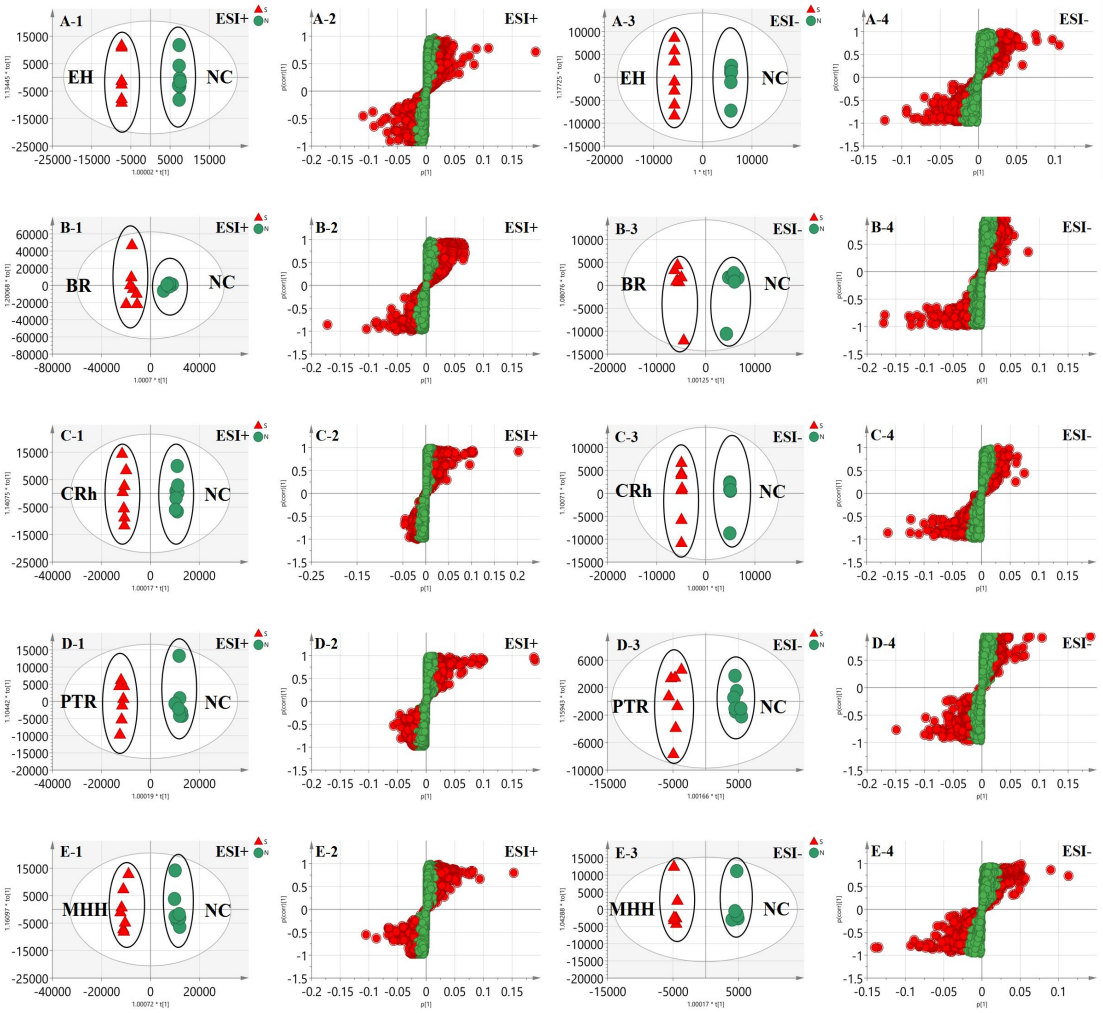
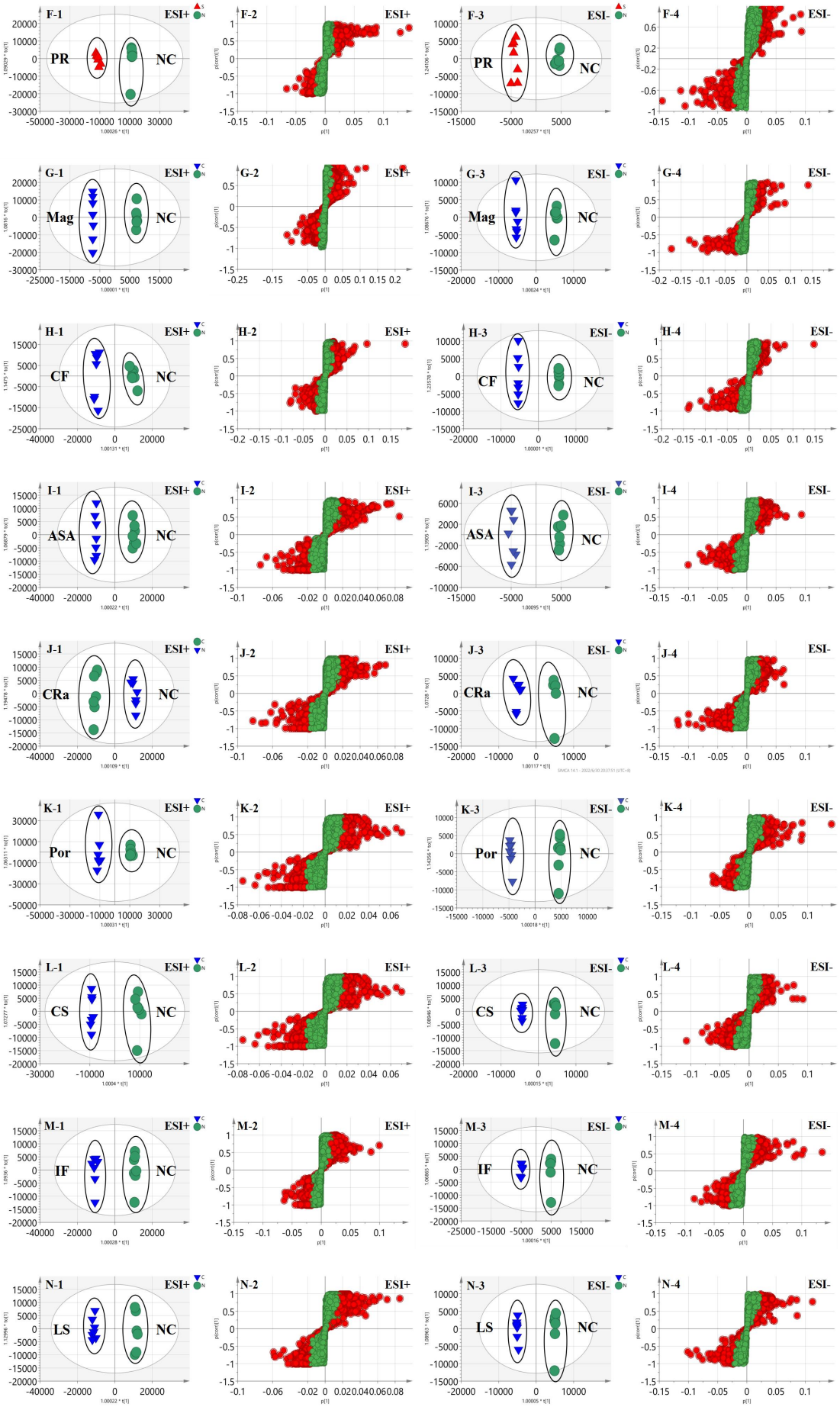


Fig. S 7 OPLS-DA score plots and S-plots in negative ion mode obtained from liver sample

(EH: *Ephedrae Herba*; BR: *Bupleuri Radix*; CRh: *Cimicifugae Rhizoma*; PTR: *Puerariae Thomsonii Radix*; MHH: *Menthae Haplocalycis Herba*; PR: *Platycodonis Radix*; Mag: *Magnetitum*; CF: *Caryophylli Flos*; ASA: *Armeniacae Semen Amarum*; CRa: *Cyathulae Radix*; Por: *Poria*; CS: *Canavaliae Semen*; IF: *Inulae Flos*; LS: *Lepidii Semen*; CR: *Chuanxiong Rhizoma*)

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G-3
ESI-
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ESI-
CF
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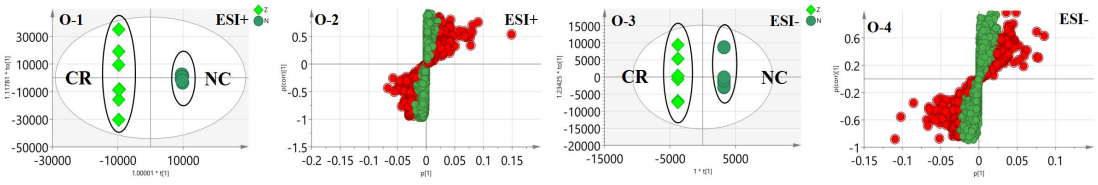
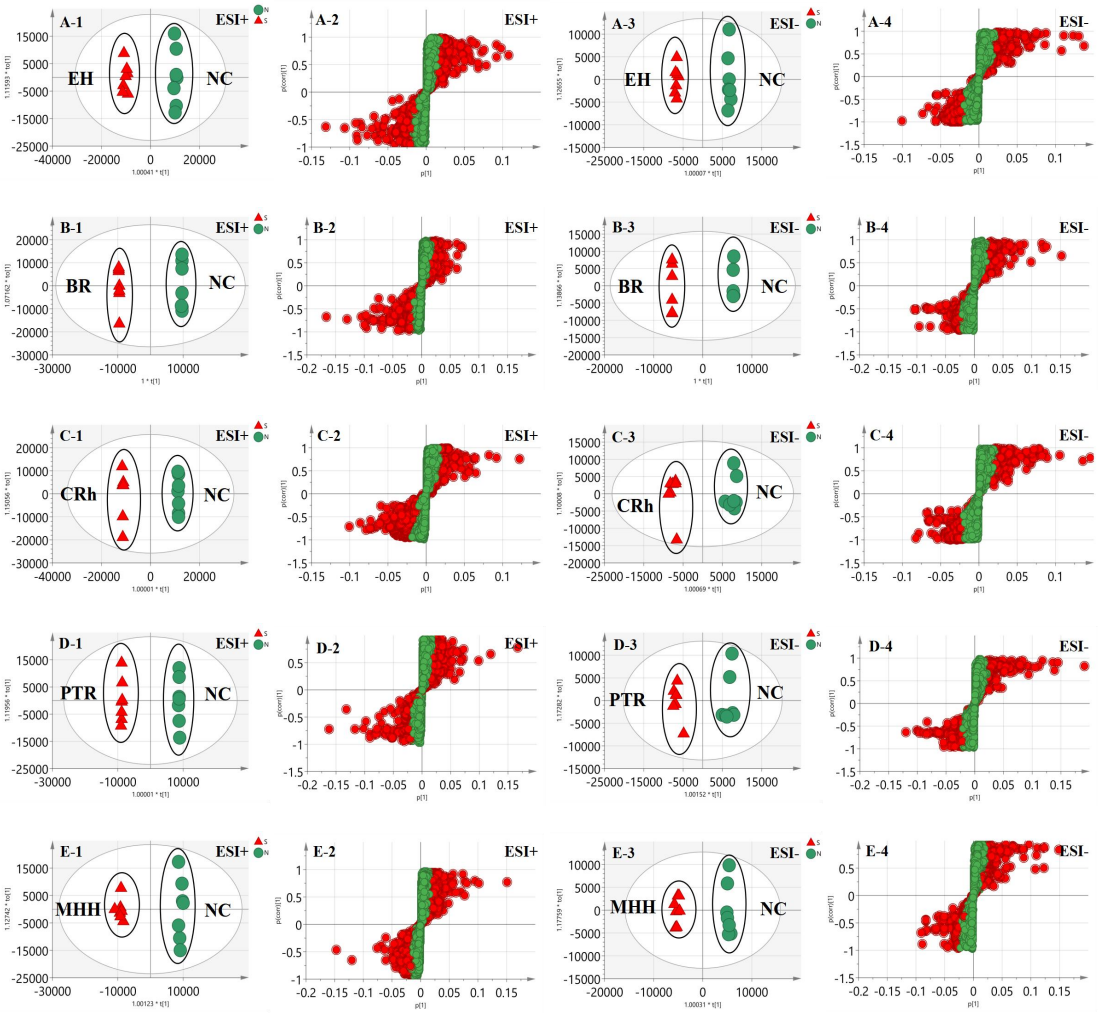
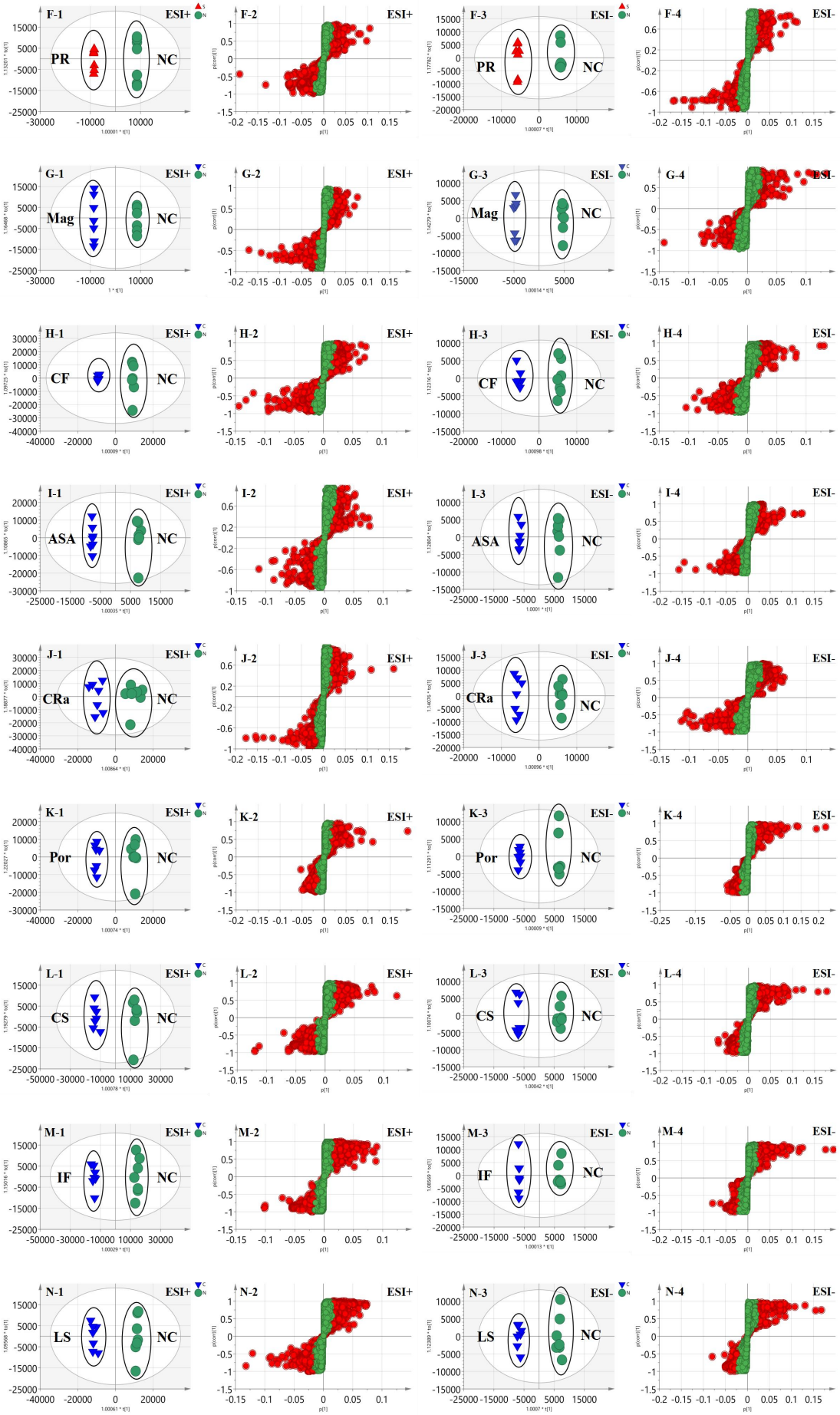


Fig. S 8 OPLS-DA score plots and S-plots obtained from lung sample (EH: *Ephedrae Herba*; BR: *Bupleuri Radix*; CRh: *Cimicifugae Rhizoma*; PTR: *Puerariae Thomsonii Radix*; MHH: *Menthae Haplocalycis Herba*; PR: *Platycodonis Radix*; Mag: *Magnetitum*; CF: *Caryophylli Flos*; ASA: *Armeniacae Semen Amarum*; CRa: *Cyathulae Radix*; Por: *Poria*; CS: *Canavaliae Semen*; IF: *Inulae Flos*; LS: *Lepidii Semen*; CR: *Chuanxiong Rhizoma*)

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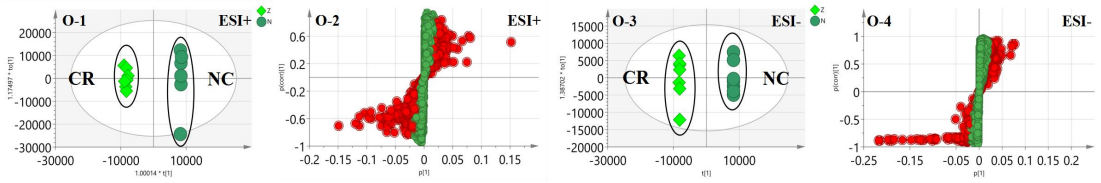
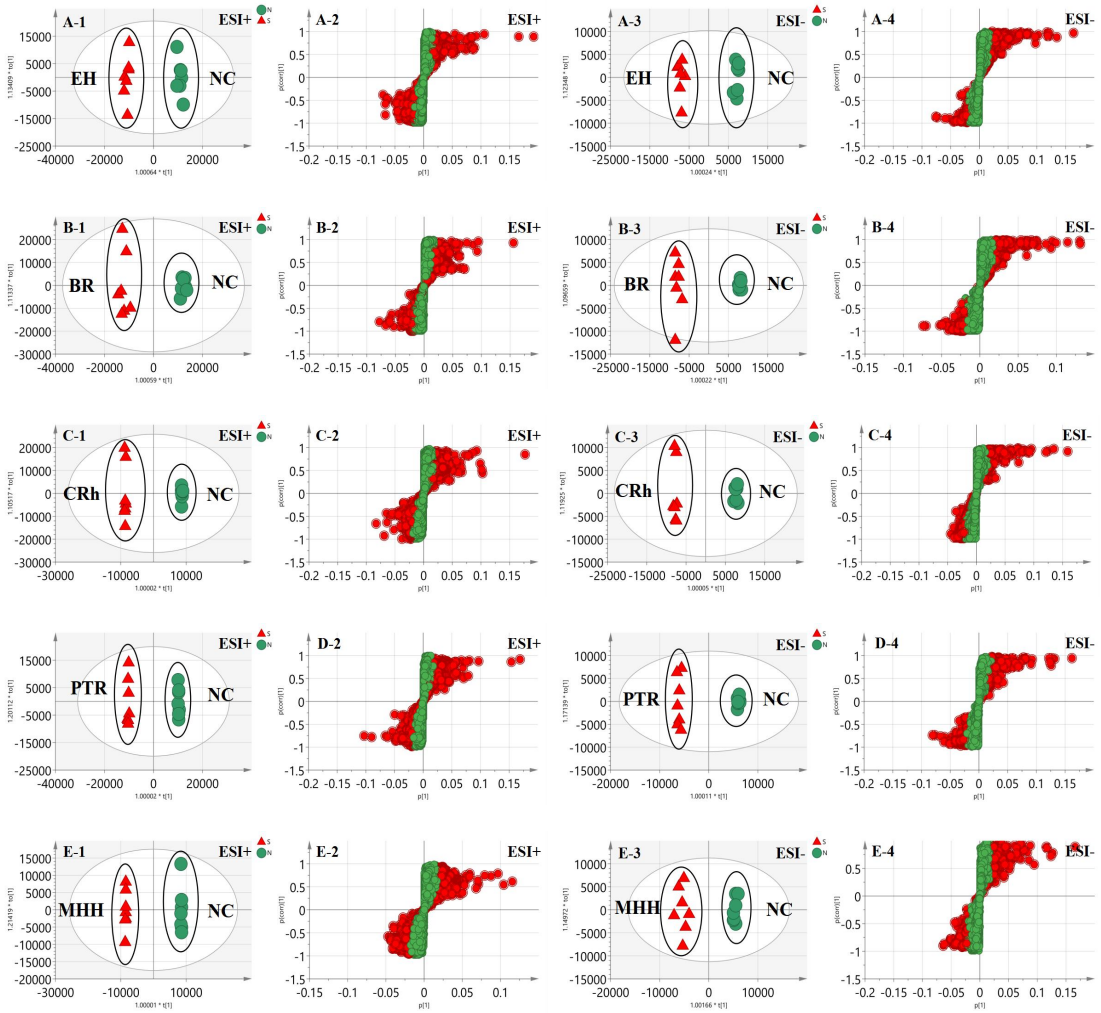
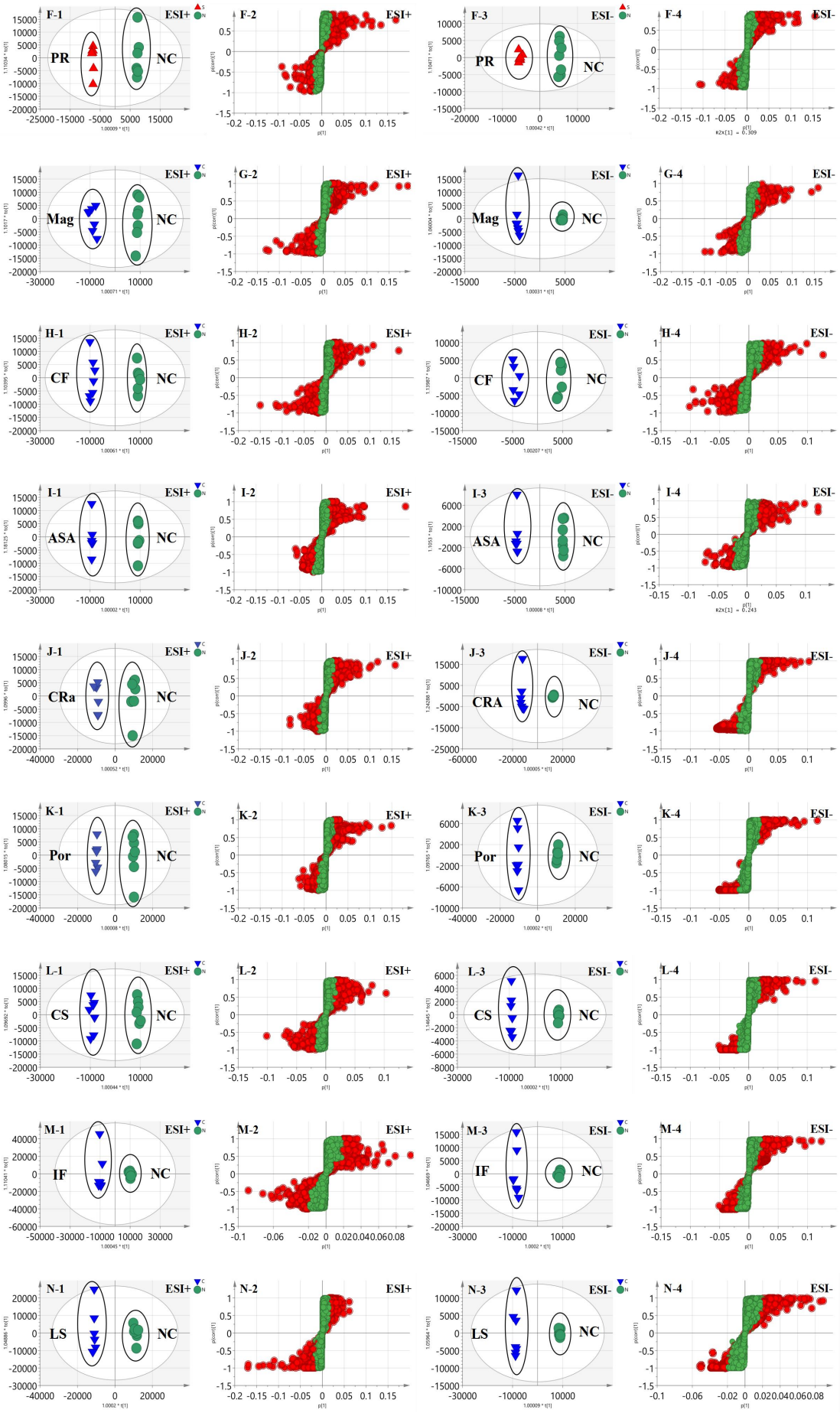


Fig. S 9 OPLS-DA score plots and S-plots obtained from kidney sample (EH: *Ephedrae Herba*; BR: *Bupleuri Radix*; CRh: *Cimicifugae Rhizoma*; PTR: *Puerariae Thomsonii Radix*; MHH: *Menthae Haplocalycis Herba*; PR: *Platycodonis Radix*; Mag: *Magnetitum*; CF: *Caryophylli Flos*; ASA: *Armeniacae Semen Amarum*; CRa: *Cyathulae Radix*; Por: *Poria*; CS: *Canavaliae Semen*; IF: *Inulae Flos*; LS: *Lepidii Semen*; CR: *Chuanxiong Rhizoma*)

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CF
NC
H-2
ESI+
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ESI-
CF
NC
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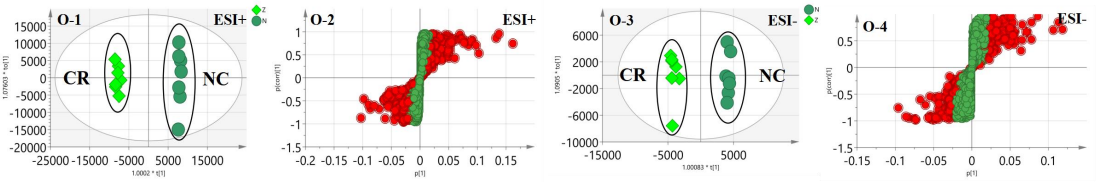
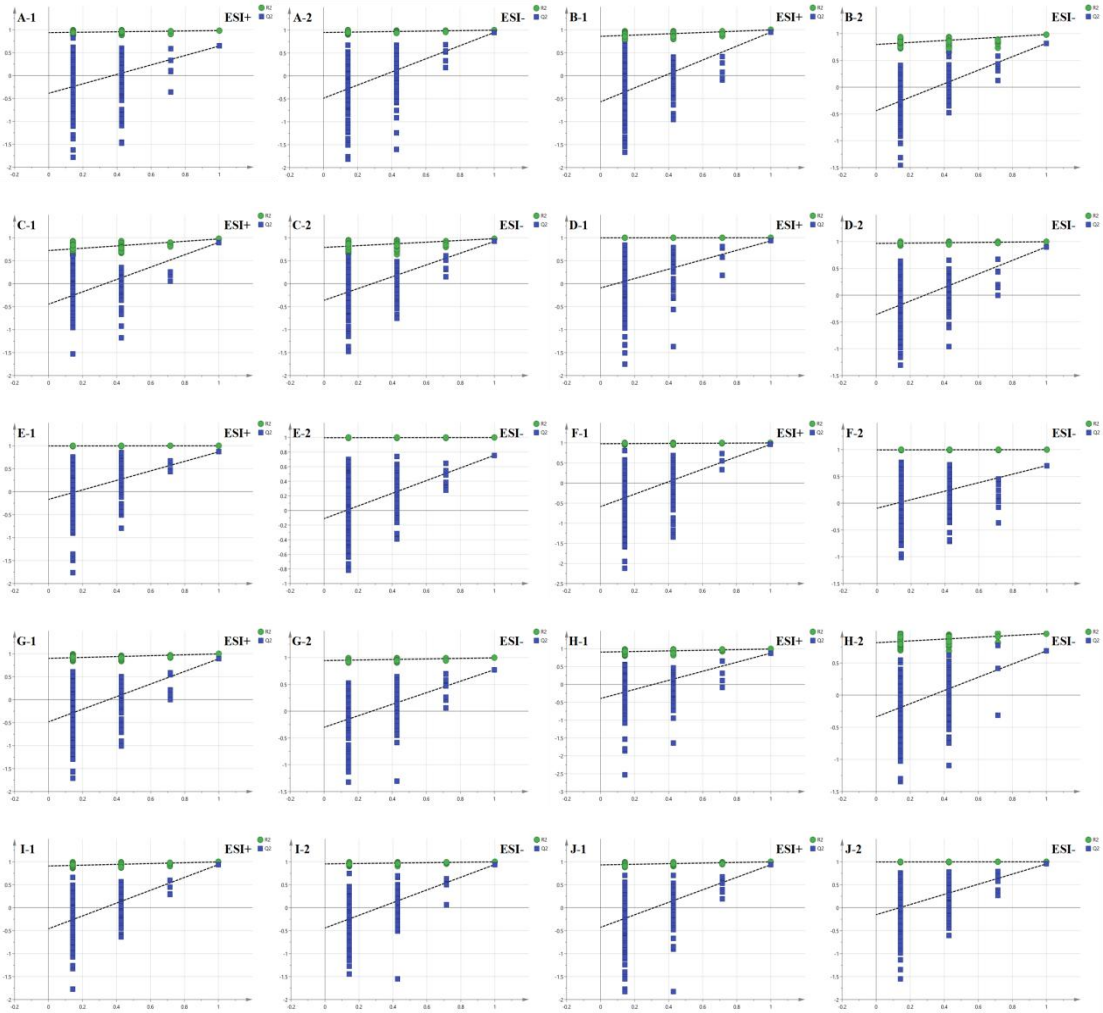


Fig. S 10 OPLS-DA score plots and S-plots obtained from spleen sample

(EH: *Ephedrae Herba*; BR: *Bupleuri Radix*; CRh: *Cimicifugae Rhizoma*; PTR: *Puerariae Thomsonii Radix*; MHH: *Menthae Haplocalycis Herba*; PR: *Platycodonis Radix*; Mag: *Magnetitum*; CF: *Caryophylli Flos*; ASA: *Armeniacae Semen Amarum*; CRa: *Cyathulae Radix*; Por: *Poria*; CS: *Canavaliae Semen*; IF: *Inulae Flos*; LS: *Lepidii Semen*; CR: *Chuanxiong Rhizoma*)



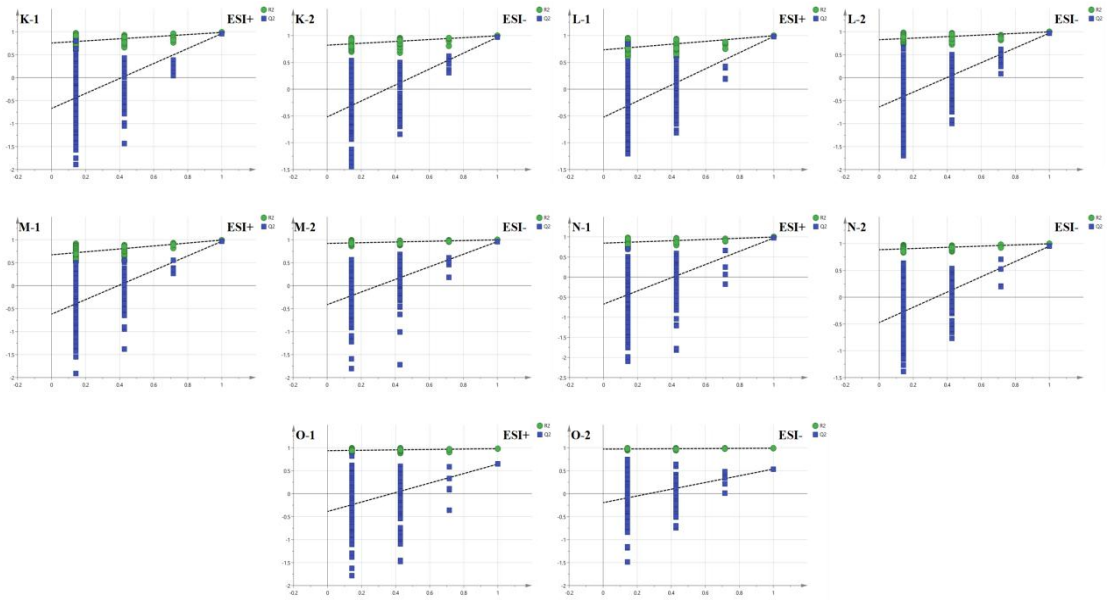
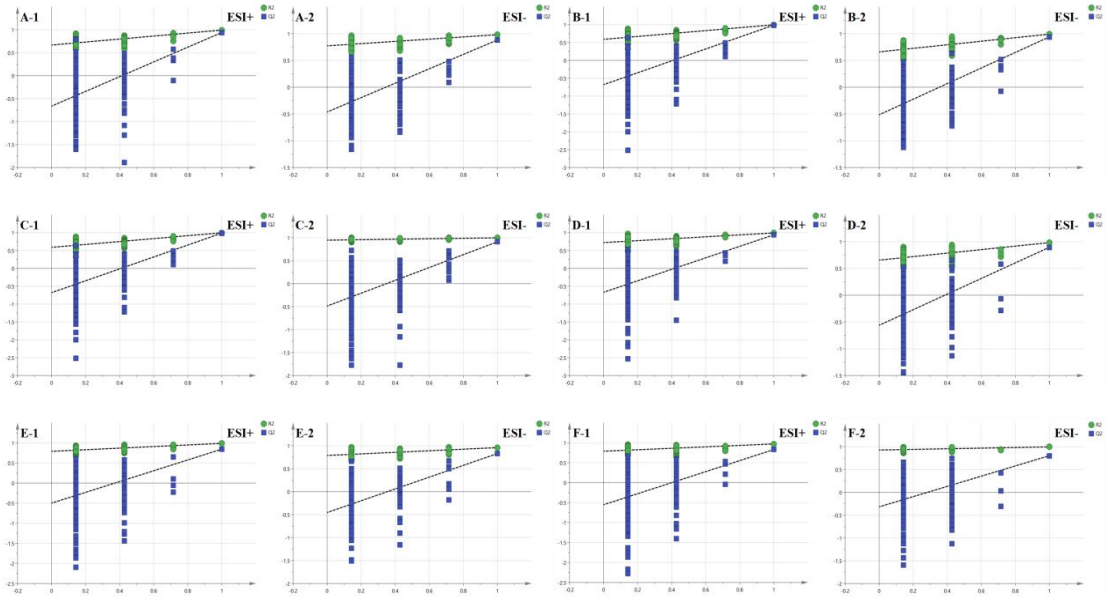


Fig. S 11 permutation test of control group and administration group in heart sample

(A: *Ephedrae Herba*; B: *Bupleuri Radix*; C: *Cimicifugae Rhizoma*; D: *Puerariae Thomsonii Radix*; E: *Menthae Haplocalycis Herba*; F: *Platycodonis Radix*; G: *Magnetitum*; H: *Caryophylli Flos*; I: *Armeniacae Semen Amarum*; J: *Cyathulae Radix* ; K: *Poria*; L: *Canavaliae Semen*; M: *Inulae Flos*; N: *Lepidii Semen*; O: *Chuanxiong Rhizoma*)



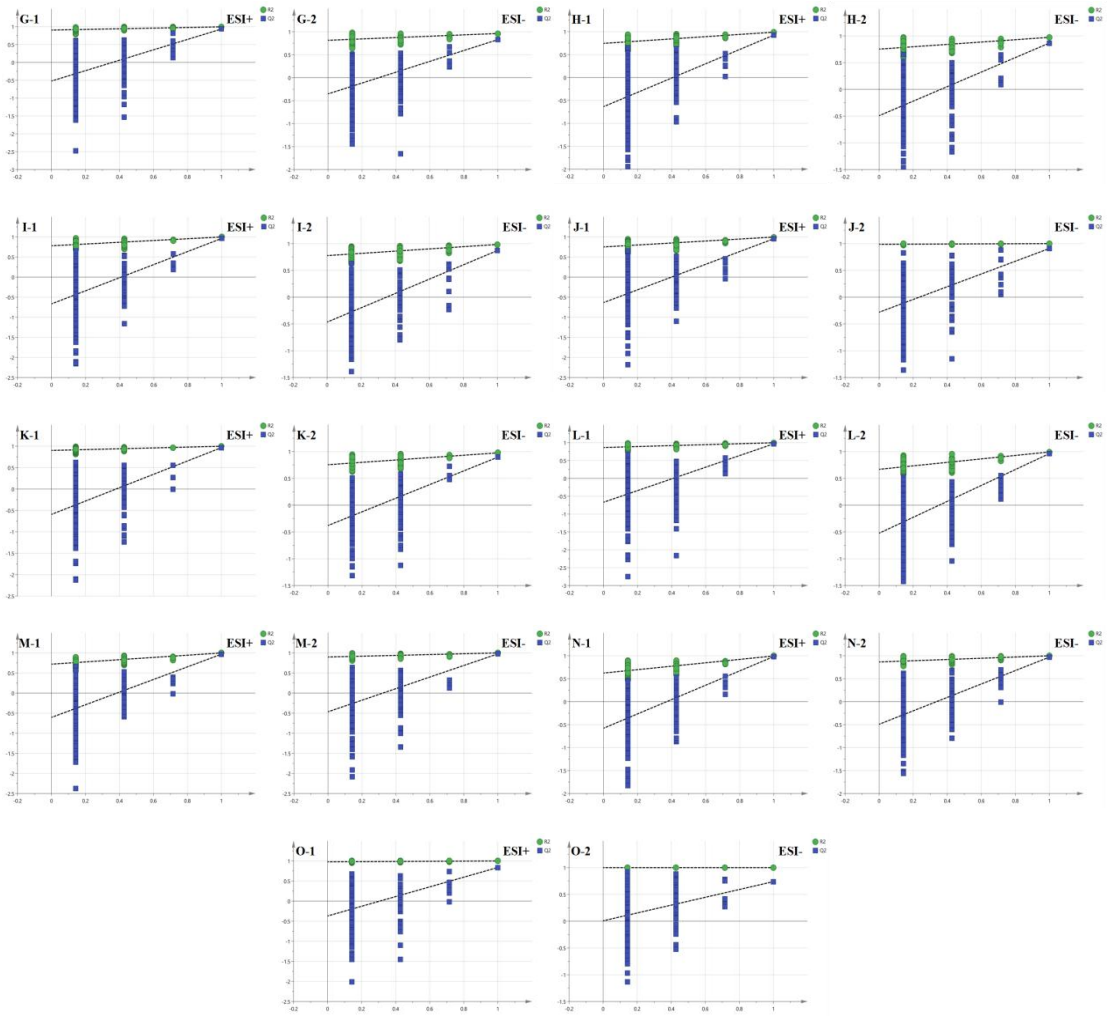
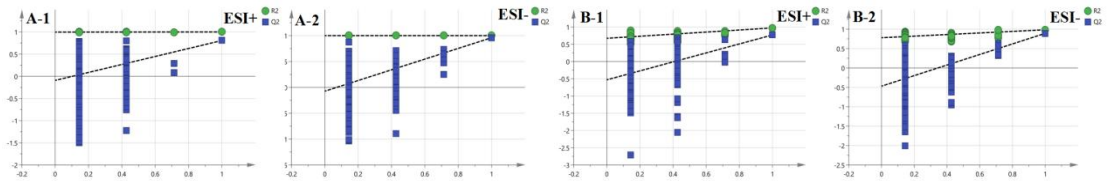


Fig. S 12 permutation test of control group and administration group in liver sample

(A: *Ephedrae Herba*; B: *Bupleuri Radix*; C: *Cimicifugae Rhizoma*; D: *Puerariae Thomsonii Radix*; E: *Menthae Haplocalycis Herba*; F: *Platycodonis Radix*; G: *Magnetitum*; H: *Caryophylli Flos*; I: *Armeniacae Semen Amarum*; J: *Cyathulae Radix* ; K: *Poria*; L: *Canavaliae Semen*; M: *Inulae Flos*; N: *Lepidii Semen*; O: *Chuanxiong Rhizoma*)



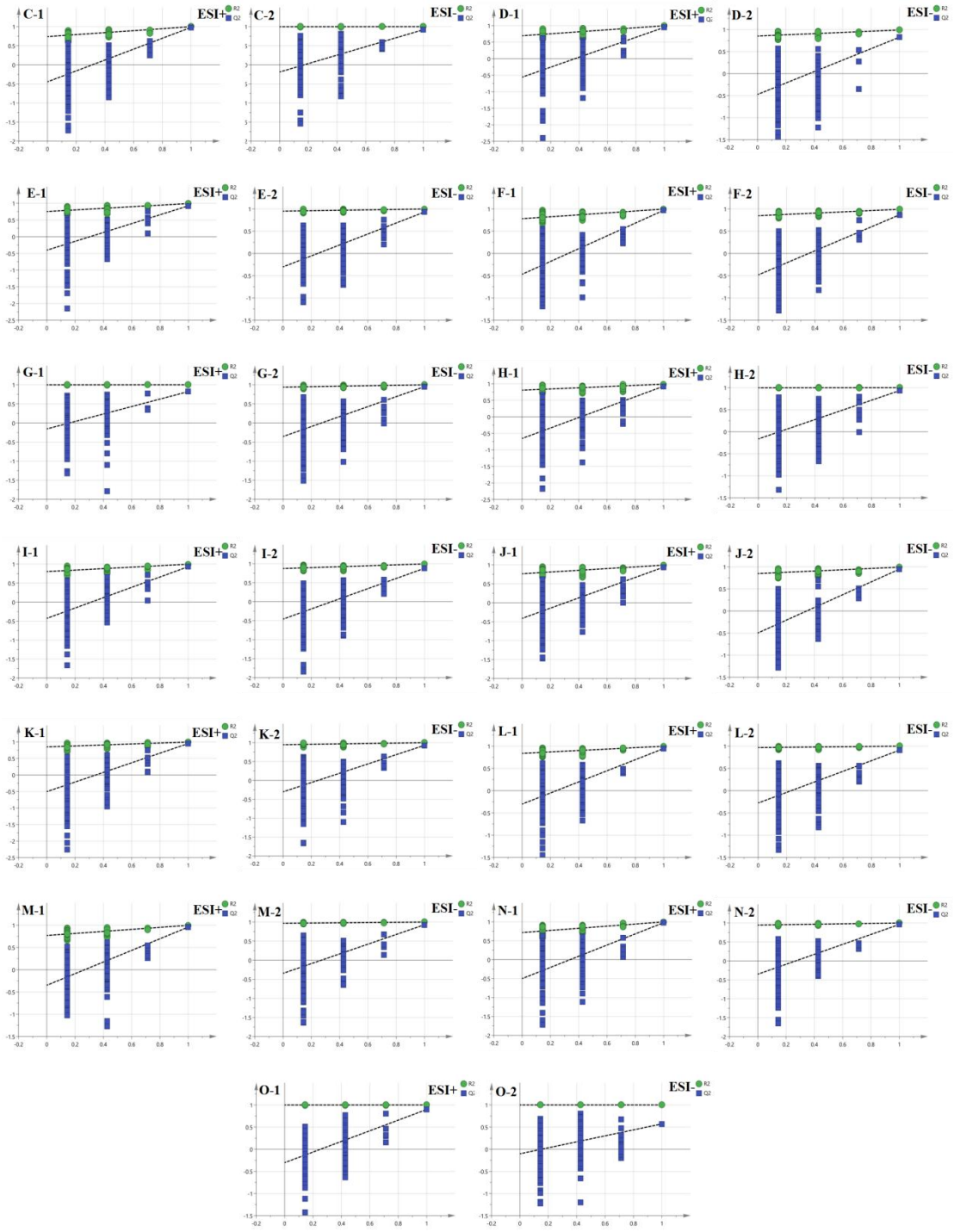


Fig. S 13 permutation test of control group and administration group in lung sample

(A: *Ephedrae Herba*; B: *Bupleuri Radix*; C: *Cimicifugae Rhizoma*; D: *Puerariae Thomsonii Radix*; E: *Menthae Haplocalycis Herba*; F: *Platycodonis Radix*; G: *Magnetitum*; H: *Caryophylli Flos*; I: *Armeniacae Semen Amarum*; J: *Cyathulae Radix* ; K: *Poria*; L: *Canavaliae Semen*; M: *Inulae Flos*; N: *Lepidii Semen*; O: *Chuanxiong*

Rhizoma)

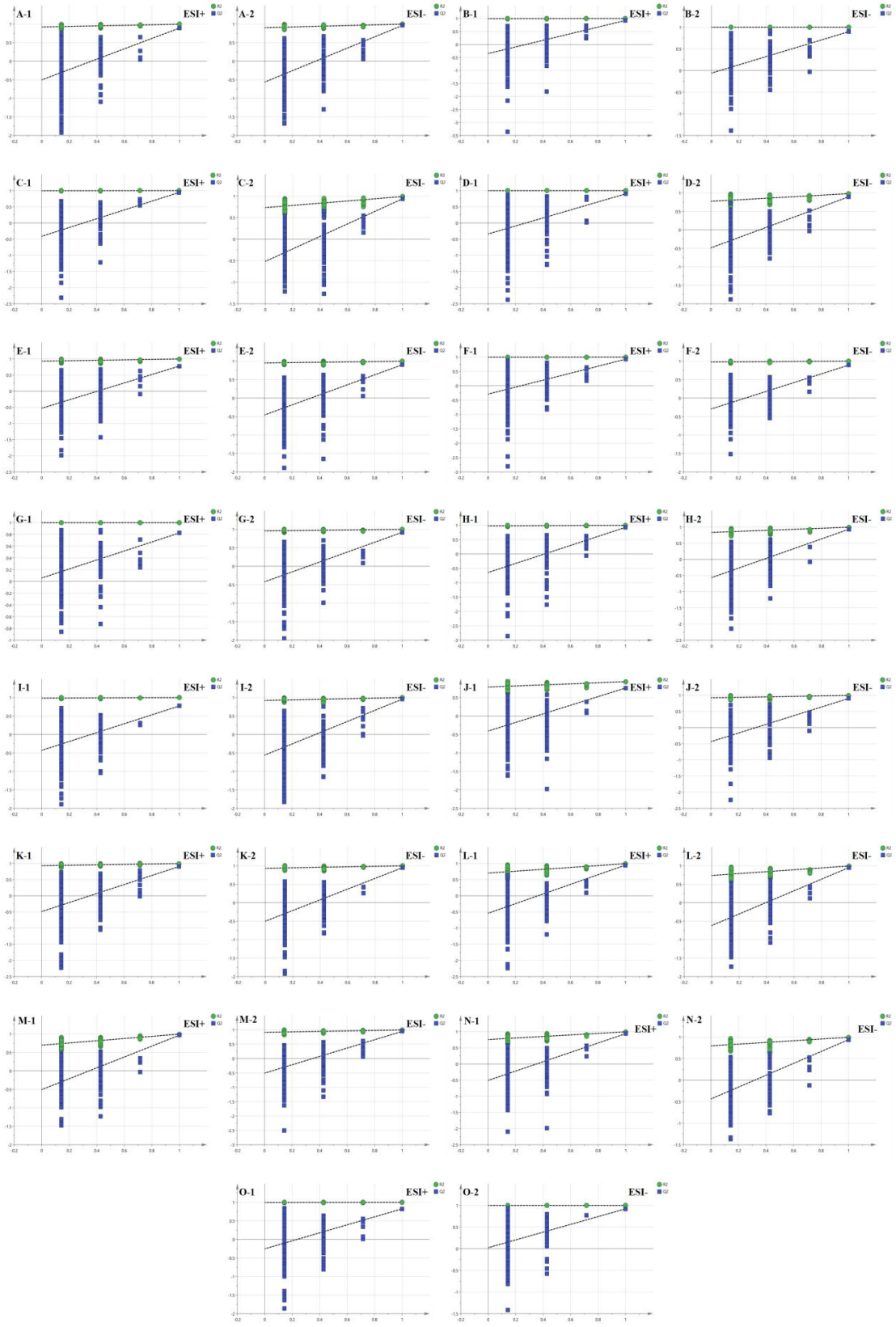
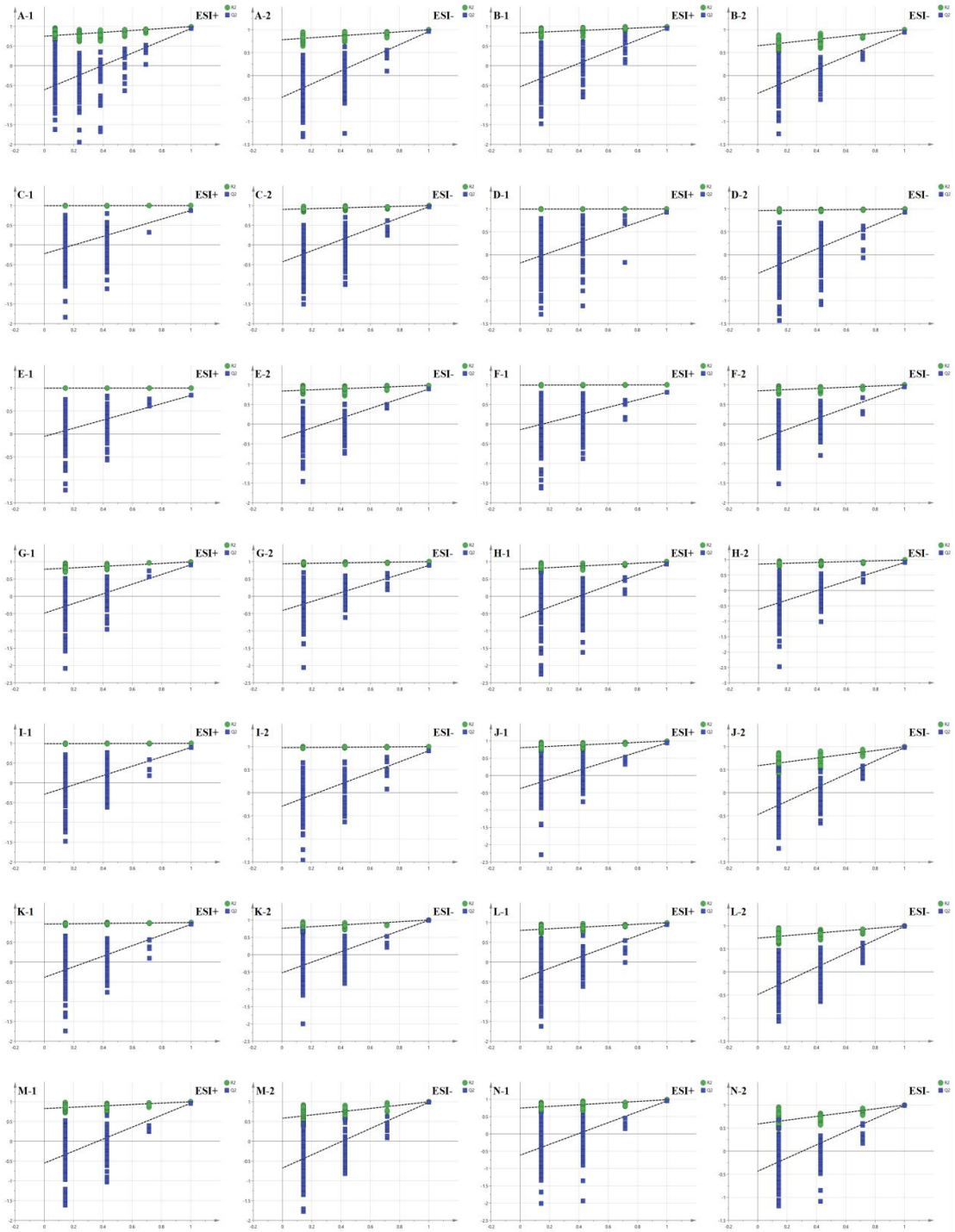


Fig. S 14 permutation test of control group and administration group in kidney sample

(A: *Ephedrae Herba*; B: *Bupleuri Radix*; C: *Cimicifugae Rhizoma*; D: *Puerariae Thomsonii Radix*; E: *Menthae Haplocalycis Herba*; F: *Platycodonis Radix*; G: *Magnetitum*; H: *Caryophylli Flos*; I: *Armeniacae Semen Amarum*; J: *Cyathulae Radix* ; K: *Poria*; L: *Canavaliae Semen*; M: *Inulae Flos*; N: *Lepidii Semen*; O: *Chuanxiong Rhizoma*)



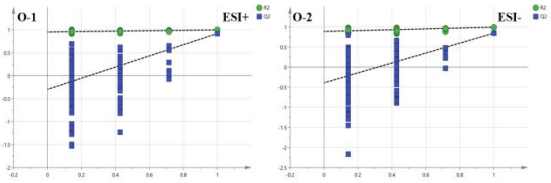


Fig. S 15 permutation test of control group and administration group in spleen sample

(A: *Ephedrae Herba*; B: *Bupleuri Radix*; C: *Cimicifugae Rhizoma*; D: *Puerariae Thomsonii Radix*; E: *Menthae Haplocalycis Herba*; F: *Platycodonis Radix*; G: *Magnetitum*; H: *Caryophylli Flos*; I: *Armeniacae Semen Amarum*; J: *Cyathulae Radix* ; K: *Poria*; L: *Canavaliae Semen*; M: *Inulae Flos*; N: *Lepidii Semen*; O: *Chuanxiong Rhizoma*)

Table S 1 Information of potential biomarkers in heart sample

Mode	Accurate Mass (m/z)	Proposed Identify	Formula	KEEEG ID	Metabolic pathways
ESI+					
1	104.1075	Choline	$C_5H_{14}NO$	C00114	Glycine, serine and threonine metabolism
2	117.079	Betaine	$C_5H_{11}NO_2$	C00719	Glycine, serine and threonine metabolism
3	122.048	Niacinamide	$C_6H_6N_2O$	C00153	Nicotinate and nicotinamide metabolism
4	125.0147	Taurine	$C_2H_7NO_3S$	C00245	Taurine and hypotaurine metabolism
5	128.0586	5,6-dihydrothymine	$C_5H_8N_2O_2$	C00906	
6	129.0426	Pyroglutamic acid	$C_5H_7NO_3$	C01877	Arginine and proline metabolism
7	131.0695	Creatine	$C_4H_9N_3O_2$	C00300	Glycine, serine and threonine metabolism
8	131.0946	Leucine	$C_6H_{13}NO_2$	C16439	2-Oxocarboxylic acid metabolism
9	113.0589	Creatinine	$C_4H_7N_3O$	C00791	Arginine and proline metabolism
10	136.0385	Hypoxanthine	$C_5H_4N_4O$	C00262	Purine metabolism
11	137.0715	1-Methylnicotinamide	$C_7H_9N_2O$	C02918	Nicotinate and nicotinamide metabolism
12	146.1181	Acetylcholine	$C_7H_{16}NO_2$	C01996	Glycerophospholipid metabolism
13	146.0691	L-Glutamine	$C_5H_{10}N_2O_3$	C00064	Purine metabolism
14	147.0532	Glutamic acid	$C_5H_9NO_4$	C00302	Glutathione metabolism
15	160.1338	Methacholine	$C_8H_{18}NO_2$	C00073	L-Methionine
16	161.1052	L-Carnitine	$C_7H_{15}NO_3$	C00318	Bile secretion
17	165.079	L-Phenylalanine	$C_9H_{11}NO_2$	C00079	Phenylalanine metabolism
18	174.1117	Arginine	$C_6H_{14}N_4O_2$	C02385	Arginine and proline metabolism
19	181.0739	Tyrosine	$C_9H_{11}NO_3$	C00082	Tyrosine metabolism
20	180.0634	myo-Inositol	$C_6H_{12}O_6$	C00137	Galactose metabolism
21	204.1236	L-Acetylcarnitine	$C_9H_{18}NO_4$		

22	204.0899	Tryptophan	$C_{11}H_{12}N_2O_2$	C00078	Tryptophan metabolism
23	219.1107	Pantothenic acid	$C_9H_{17}NO_5$	C00864	beta-Alanine metabolism
24	267.0968	Adenosine	$C_{10}H_{13}N_5O_4$	C00212	Purine metabolism
25	268.0808	Inosine	$C_{10}H_{12}N_4O_5$	C00294	Purine metabolism
26	299.2824	Sphingosine	$C_{18}H_{37}NO_2$	C00319	Sphingolipid metabolism
27	280.2402	Linoleate	$C_{18}H_{32}O_2$	C01595	Linoleic acid metabolism
28	306.2559	Dihomo-gamma-linolenate	$C_{20}H_{34}O_2$	C03242	Linoleic acid metabolism
29	307.0838	Glutathione	$C_{10}H_{17}N_3O_6S$	C00051	Glutathione metabolism
30	315.241	Decanoylcarnitine	$C_{17}H_{33}NO_4$		
31	369.2879	trans-2-Tetradecenoylcarnitine	$C_{21}H_{39}NO_4$		
32	371.3036	Tetradecanoylcarnitine	$C_{21}H_{42}NO_4$		
33	385.3192	10,20-Dihydroxyeicosanoic acid	$C_{22}H_{43}NO_4$		
34	395.3036	9,12-Hexadecadienoylcarnitine	$C_{23}H_{41}NO_4$		
35	396.3028	delta-Tocotrienol	$C_{27}H_{40}O_2$	C14156	
36	397.3192	9-Hexadecenoylcarnitine	$C_{23}H_{43}NO_4$		
37	416.329	Secalciferol	$C_{27}H_{44}O_3$	C07712	Steroid biosynthesis
38	399.3349	Palmitoylcarnitine	$C_{23}H_{45}NO_4$		Fatty acid metabolism
39	400.3341	Calcidiol	$C_{27}H_{44}O_2$	C01561	Steroid biosynthesis
40	413.3505	Heptadecanoyl carnitine	$C_{24}H_{47}NO_4$		
41	415.3298	3-Hydroxyhexadecanoylcarnitine	$C_{23}H_{45}NO_5$		
42	447.3349	Arachidonoylcarnitine	$C_{27}H_{45}NO_4$		
43	427.3662	Stearoylcarnitine	$C_{25}H_{49}NO_4$		
44	858.7676	TG(16:0/16:0/22:5(4Z,7Z,10Z,13Z,16Z))	$C_{55}H_{102}O_6$		
45	452.3654	2',3'-Dihydro-phytomenadione	$C_{31}H_{48}O_2$		
46	453.3818	N-Nervonoyl Serine	$C_{27}H_{51}NO_4$		
47	481.3168	LysoPE(18:0/0:0)	$C_{23}H_{48}NO_7P$		
48	495.3325	LysoPC(0:0/16:0)	$C_{24}H_{50}NO_7P$		
49	519.3325	LysoPC(0:0/18:2(9Z,12Z))	$C_{26}H_{50}NO_7P$		
50	523.3638	LysoPC(0:0/18:0)	$C_{26}H_{54}NO_7P$		
51	503.3012	LysoPE(22:6(4Z,7Z,10Z,13Z,16Z,19Z)/0:0)	$C_{25}H_{46}NO_7P$		
ESI-					
1	118.0266	Succinate	$C_4H_6O_4$	C00042	Citrate cycle (TCA cycle)
2	132.0535	L-Asparagine	$C_4H_8N_2O_3$		Alanine, aspartate and glutamate metabolism
3	134.0215	Malic acid	$C_4H_6O_5$	C00149	Citrate cycle (TCA cycle)
4	152.0334	Xanthine	$C_5H_4N_4O_2$	C00385	Purine metabolism
5	168.0283	Urate	$C_5H_4N_4O_3$	C00366	Purine metabolism
6	206.0427	Homocitric acid	$C_7H_{10}O_7$	C01251	Pyruvate metabolism

7	172.0137	sn-Glycerol 3-phosphate	$C_3H_9O_6P$	C00620	Purine metabolism
8	256.2402	Palmitic acid	$C_{16}H_{32}O_2$	C00249	Fatty acid metabolism
9	260.0297	myo-Inositol 1-phosphate	$C_6H_{13}O_9P$	C01177	Inositol phosphate metabolism
10	280.2402	Malvalic acid	$C_{18}H_{32}O_2$	C08321	
11	282.2559	Oleic acid	$C_{18}H_{34}O_2$	C00712	Fatty acid biosynthesis
12	304.2402	Arachidonate	$C_{20}H_{32}O_2$	C00219	Arachidonic acid metabolism
13	323.957	Trichloroethanol glucuronide	$C_8H_{11}Cl_3O_7$	C14869	Metabolism of xenobiotics by cytochrome P450
14	328.2402	Docosahexaenoic acid	$C_{22}H_{32}O_2$	C06429	Biosynthesis of unsaturated fatty acids
15	328.2614	MG(16:1(9Z)/0:0/0:0)	$C_{19}H_{36}O_4$		
16	330.2559	4,8,12,15,19-Docosapentaenoic acid	$C_{22}H_{34}O_2$		Biosynthesis of unsaturated fatty acids
17	332.2715	Adrenic acid	$C_{22}H_{36}O_2$	C16527	Biosynthesis of unsaturated fatty acids
18	437.2906	LysoPE(P-16:0/0:0)	$C_{21}H_{44}NO_6P$		
19	454.2931	DG(20:3(8Z,11Z,14Z)-2OH(5,6)/0:0/2:0)	$C_{25}H_{42}O_7$		
20	477.2855	LysoPE(18:2(9Z,12Z)/0:0)	$C_{23}H_{44}NO_7P$		
21	527.3012	LysoPE(22:5(7Z,10Z,13Z,16Z,19Z)/0:0)	$C_{27}H_{46}NO_7P$		

Table S 2 Information of potential biomarkers in liver sample

Mode	Accurate Mass (m/z)	Proposed Identify	Formula	KEEEG ID	Metabolic pathways
ESI+					
1	104.1075	Choline	$C_5H_{14}NO$	C00114	Glycine. serine and threonine metabolism
2	115.0633	Proline	$C_5H_9NO_2$	C16435	Arginine and proline metabolism
3	117.079	Betaine	$C_5H_{11}NO_2$	C00719	Glycine. serine and threonine metabolism
4	121.0891	Phenethylamine	$C_8H_{11}N$	C05332	Phenylalanine metabolism
5	122.048	Niacinamide	$C_6H_6N_2O$	C00153	Nicotinate and nicotinamide metabolism
6	129.0426	1-Pyrroline-4-hydroxy-2-carboxylate	$C_5H_7NO_3$	C04282	Arginine and proline metabolism
7	131.0695	Creatine	$C_4H_9N_3O_2$	C00300	Arginine and proline metabolism
8	131.0946	L-Leucine	$C_6H_{13}NO_2$	C00123	Aminoacyl-tRNA biosynthesis
9	132.0899	Ornithine	$C_5H_{12}N_2O_2$	C01602	Arginine and proline metabolism
10	133.0375	Aspartic acid	$C_4H_7NO_4$	C16433	Alanine. aspartate and glutamate metabolism
11	135.0684	2-Phenylacetamide	C_8H_9NO	C02505	Phenylalanine metabolism
12	136.0385	Hypoxanthine	$C_5H_4N_4O$	C00262	Purine metabolism
13	145.0851	Acetylcholine	$C_5H_{11}N_3O_2$	C01996	Glycerophospholipid metabolism
14	146.0691	L-Glutamine	$C_5H_{10}N_2O_3$	C00064	Purine metabolism
15	147.0532	L-Glutamate	$C_5H_9NO_4$	C00025	Alanine, aspartate and glutamate metabolism
16	149.051	L-Methionine	$C_5H_{11}NO_2S$	C00073	Cysteine and methionine metabolism
17	155.0695	L-Histidine	$C_6H_9N_3O_2$	C00135	Histidine metabolism
18	161.1052	L-Carnitine	$C_7H_{15}NO_3$	C00318	Bile secretion

19	165.079	L-Phenylalanine	$C_9H_{11}NO_2$	C00079	Phenylalanine metabolism
20	150.0317	alpha-Oxo-benzeneaceticac id	$C_8H_6O_3$		
21	181.0739	Tyrosine	$C_9H_{11}NO_3$	C00082	Tyrosine metabolism
22	161.0841	Tryptophol	$C_{10}H_{11}NO$	C00955	Tryptophan metabolism
23	180.0634	L-Galactose	$C_6H_{12}O_6$	C01825	D-Fructose
24	184.0739	Phosphorylcholine	$C_5H_{15}NO_4P$	C00588	Glycerophospholipid metabolism
25	217.1314	Propionylcarnitine	$C_{10}H_{19}NO_4$	C03017	
26	257.1028	Glycerophosphocholine	$C_8H_{20}NO_6P$	C00670	Glycerophospholipid metabolism
27	268.0808	Inosine	$C_{10}H_{12}N_4O_5$	C00294	Purine metabolism
28	187.1685	N1-Acetylspermidin	$C_9H_{21}N_3O$	C00612	
29	281.2719	Oleamide	$C_{18}H_{35}NO$	C19670	
30	302.2246	Retinyl ester	$C_{20}H_{30}O_2$	C02075	Retinol metabolism
31	304.2402	Arachidonic acid	$C_{20}H_{32}O_2$	C00219	Arachidonic acid metabolism
32	307.0838	Glutathione	$C_{10}H_{17}N_3O_6S$	C00051	Glutathione metabolism
33	317.293	Phytosphingosine	$C_{18}H_{39}NO_3$	C12144	Sphingolipid metabolism
34	399.3349	Palmitoylcarnitine	$C_{23}H_{45}NO_4$	C02990	Fatty acid metabolism
35	427.3662	Stearoylcarnitine	$C_{25}H_{49}NO_4$		
36	390.2042	Prostratin	$C_{22}H_{30}O_6$	C20197	
37	447.3349	Arachidonoylcarnitine	$C_{27}H_{45}NO_4$		
38	449.3141	Chenodeoxyglycocholic acid	$C_{26}H_{43}NO_5$		
39	481.3168	LysoPC(15:0/0:0)	$C_{23}H_{48}NO_7P$		Lysophospholipid metabolism
40	495.3325	LysoPC(16:0/0:0)	$C_{24}H_{50}NO_7P$		Lysophospholipid metabolism
41	543.3325	LysoPC(20:4(8Z,11Z,14Z, 17Z)/0:0)	$C_{28}H_{50}NO_7P$		Lysophospholipid metabolism
42	280.2402	Octadecadienoate	$C_{18}H_{32}O_2$	C01595	Linoleic acid metabolism
ESI-					
1	104.0473	2-Hydroxybutyric acid	$C_4H_8O_3$	C05984	Propanoate metabolism
2	116.011	Fumarate	$C_4H_4O_4$	C00122	Citrate cycle (TCA cycle)
3	118.0266	Succinate	$C_4H_6O_4$	C00042	Citrate cycle
4	119.0582	L-Threonine	$C_4H_9NO_3$	C00188	Glycine, serine and threonine metabolism
5	125.0147	Taurine	$C_2H_7NO_3S$	C00245	Taurine and hypotaurine metabolism
6	132.0423	Glutaric acid	$C_5H_8O_4$	C00489	
7	152.0334	Xanthine	$C_5H_4N_4O_2$	C00385	Purine metabolism
8	168.0283	Urate	$C_5H_4N_4O_3$	C00366	Purine metabolism
9	174.0164	Cis-Aconitate	$C_6H_6O_6$	C00417	Citrate cycle (TCA cycle)
10	204.0899	L-Tryptophan	$C_{11}H_{12}N_2O_2$	C00078	Glycine, serine and threonine metabolism
11	215.0559	3-Phospho-D-glycerate	$C_5H_{14}NO_6P$	C00197	Glycerophospholipid metabolism
12	219.1107	Pantothenic acid	$C_9H_{17}NO_5$	C00864	beta-Alanine metabolism
13	230.0192	L-Xylulose 5-phosphate	$C_5H_{11}O_8P$	C00231	Purine metabolism
14	270.0964	Aspartyl-Histidine	$C_{10}H_{14}N_4O_5$		
15	290.0403	D-Sedoheptulose 7-phosphate	$C_7H_{15}O_{10}P$	C05382	Biosynthesis of amino acids

16	309.106	N-Acetylneuraminic acid	$C_{11}H_{19}NO_9$	C00270	Amino sugar and nucleotide sugar metabolism
17	301.2981	Sphinganine	$C_{18}H_{39}NO_2$	C00836	Sphingolipid metabolism
18	350.2457	Tetrahydrocorticosterone	$C_{21}H_{34}O_4$	C05476	Steroid hormone biosynthesis
19	389.9518	Phosphoribosyl pyrophosphate	$C_5H_{13}O_{14}P_3$		Histidine metabolism
20	453.2855	LysoPE(0:0/16:0)	$C_{21}H_{44}NO_7P$		Lysophospholipid metabolism
21	465.309	Glycocholic acid	$C_{26}H_{43}NO_6$	C01921	Bile secretion
22	515.2917	Taurocholic acid	$C_{26}H_{45}NO_7S$	C05122	Taurine and hypotaurine metabolism
23	525.2855	LysoPE(0:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	$C_{27}H_{44}NO_7P$		Lysophospholipid metabolism
24	596.2962	LysoPI(18:2(9Z,12Z)/0:0)	$C_{27}H_{49}O_{12}P$		Lysophospholipid metabolism

Table S 3 Information of potential biomarkers in lung sample

Mode	Accurate Mass (m/z)	Proposed Identify	Formula	KEEEG ID	Metabolic pathways
ESI+					
1	103.0997	Choline	$C_5H_{13}NO$	C00114	Glycine, serine and threonine metabolism
2	115.0633	L-Proline	$C_5H_9NO_2$	C00148	Arginine and proline metabolism
3	137.0841	Tyramine	$C_8H_{11}NO$	C00483	Tyrosine metabolism
4	129.0426	Pyroglutamic acid	$C_5H_7NO_3$	C01879	Glutathione metabolism
5	131.0946	L-Isoleucine	$C_6H_{13}NO_2$	C00407	Cyanoamino acid metabolism
6	113.0589	Creatinine	$C_4H_7N_3O$	C00791	Arginine and proline metabolism
7	135.0684	2-Phenylacetamide	C_8H_9NO	C02505	Phenylalanine metabolism
8	136.0385	Hypoxanthine	$C_5H_4N_4O$	C00262	Purine metabolism
9	146.0691	L-Glutamine	$C_5H_{10}N_2O_3$	C00064	Purine metabolism
10	132.0535	L-Asparagine	$C_4H_8N_2O_3$	C00152	Alanine, aspartate and glutamate metabolism
11	165.079	L-Phenylalanine	$C_9H_{11}NO_2$	C00079	Phenylalanine metabolism
12	168.0283	Urate	$C_5H_4N_4O_3$	C00366	Purine metabolism
13	174.1117	Arginine	$C_6H_{14}N_4O_2$	C02385	Arginine and proline metabolism
14	203.1158	L-Acetylcarnitine	$C_9H_{17}NO_4$		
15	204.0899	L-Tryptophan	$C_{11}H_{12}N_2O_2$	C00078	Tryptophan metabolism
16	286.2297	Vitamin A	$C_{20}H_{30}O$	C00473	Retinol metabolism
17	281.2719	3-Dehydrosphinganine	$C_{18}H_{35}NO$	C02934	Sphingolipid metabolism
18	301.2981	Sphinganine	$C_{18}H_{39}NO_2$	C00836	Sphingolipid metabolism
19	302.2246	Retinyl ester	$C_{20}H_{30}O_2$	C02075	Retinol metabolism
20	304.2402	Arachidonic acid	$C_{20}H_{32}O_2$	C00219	Arachidonic acid metabolism
21	307.0838	Glutathione	$C_{10}H_{17}N_3O_6S$	C00051	Cysteine and methionine metabolism
22	317.293	Phytosphingosine	$C_{18}H_{39}NO_3$	C12144	Sphingolipid metabolism
23	300.2897	Sphingosine	$C_{18}H_{38}NO_2$	C00319	Sphingolipid metabolism
24	352.225	Prostaglandin	$C_{20}H_{32}O_5$	C00427	Arachidonic acid metabolism
25	368.3443	Cholesterol	$C_{27}H_{44}$	C00187	Steroid biosynthesis
26	399.3349	Palmitoylcarnitine	$C_{23}H_{45}NO_4$	C02990	Fatty acid metabolism

ESI-					
1	112.0273	Uracil	$C_4H_4N_2O_2$	C00106	Pyrimidine metabolism
2	97.9769	Phosphate	H_3O_4P	C00009	Parathyroid hormone synthesis, secretion and action
3	103.0401	2-Hydroxybutyric acid	$C_4H_7O_3$	C05984	Propanoate metabolism
4	105.0426	Serine	$C_3H_7NO_3$	C00065	Glycine, serine and threonine metabolism
5	116.011	Fumarate	$C_4H_4O_4$	C00122	Citrate cycle (TCA cycle)
6	125.0147	Taurine	$C_2H_7NO_3S$	C00245	Taurine and hypotaurine metabolism
7	133.0375	L-Aspartate	$C_4H_7NO_4$	C00049	Alanine, aspartate and glutamate metabolism
8	134.0215	S-Malate	$C_4H_6O_5$	C00149	Citrate cycle (TCA cycle)
9	141.0191	O-Phosphoethanolamine	$C_2H_8NO_4P$	C00346	Glycerophospholipid metabolism
10	147.0532	L-Glutamic acid	$C_5H_9NO_4$	C00025	Alanine, aspartate and glutamate metabolism
11	152.0334	Xanthine	$C_5H_4N_4O_2$	C00385	Purine metabolism
12	155.0695	Histidine	$C_6H_9N_3O_2$	C00768	Histidine metabolism
13	174.0164	Cis-Aconitate	$C_6H_6O_6$	C00417	Citrate cycle (TCA cycle)
14	175.0481	N-Acetyl-L-aspartate	$C_6H_9NO_5$	C01042	Alanine, aspartate and glutamate metabolism
15	180.0634	Galactose	$C_6H_{12}O_6$	C01582	Galactose metabolism
16	181.0739	Tyrosine	$C_9H_{11}NO_3$	C00082	Tyrosine metabolism
17	192.027	Citrate	$C_6H_8O_7$	C00158	Citrate cycle (TCA cycle)
18	195.0895	Metyrosine	$C_{10}H_{13}NO_3$	C07921	
19	254.0573	5-L-Glutamyl-taurine	$C_7H_{14}N_2O_6S$	C05844	Taurine and hypotaurine metabolism
20	260.0297	D-Mannose 1-phosphate	$C_6H_{13}O_9P$	C00636	Fructose and mannose metabolism
21	268.0808	Inosine	$C_{10}H_{12}N_4O_5$	C00294	Purine metabolism
22	280.2402	Linoleic acid	$C_{18}H_{32}O_2$	C01595	Linoleic acid metabolism
23	282.2559	Octadecenoic acid	$C_{18}H_{34}O_2$	C00712	Fatty acid biosynthesis
24	306.2559	Dihomo-gamma-linolenic acid	$C_{20}H_{34}O_2$	C03242	Linoleic acid metabolism
25	328.2402	Docosahexaenoic acid	$C_{22}H_{32}O_2$	C06429	Biosynthesis of unsaturated fatty acids
26	347.0631	Adenosine monophosphate(AMP)	$C_{10}H_{14}N_5O_7P$	C00020	Purine metabolism
27	348.0471	Inosinic acid(IMP)	$C_{10}H_{13}N_4O_8P$	C00130	Purine metabolism
28	363.058	Guanosine monophosphate(GMP)	$C_{10}H_{14}N_5O_8P$	C00144	Purine metabolism
29	392.2927	Deoxycholic acid	$C_{24}H_{40}O_4$	C04483	Bile secretion
30	408.2876	Cholic acid	$C_{24}H_{40}O_5$	C00695	Bile secretion
31	515.2917	Taurocholate	$C_{26}H_{45}NO_7S$	C05122	Taurine and hypotaurine metabolism

Table S 4 Information of potential biomarkers in spleen sample

Mode	Accurate Mass (m/z)	Proposed Identify	Formula	KEEEG ID	Metabolic pathways
ESI+					
1	104.1075	Choline	$C_5H_{14}NO$	C00114	Glycine, serine and threonine metabolism
2	111.0433	Cytosine	$C_4H_5N_3O$	C00380	Pyrimidine metabolism
3	115.0633	Proline	$C_5H_9NO_2$	C16435	Arginine and proline metabolism
4	118.0868	Betaine	$C_5H_{12}NO_2$	C00719	Glycine, serine and threonine metabolism
5	137.0841	Tyramine	$C_8H_{11}NO$	C00483	Tyrosine metabolism
6	121.0891	Phenethylamine	$C_8H_{11}N$	C05332	Phenylalanine metabolism
7	122.048	Niacinamide	$C_6H_6N_2O$	C00153	Nicotinate and nicotinamide metabolism
8	125.0147	Taurine	$C_2H_7NO_3S$	C00245	Taurine and hypotaurine metabolism
9	131.0695	Creatine	$C_4H_9N_3O_2$	C00300	Arginine and proline metabolism
10	131.0946	Leucine	$C_6H_{13}NO_2$	C16439	2-Oxocarboxylic acid metabolism
11	133.0375	Aspartic acid	$C_4H_7NO_4$	C16433	Alanine, aspartate and glutamate metabolism
12	136.0385	Hypoxanthine	$C_5H_4N_4O$	C00262	Purine metabolism
13	145.1579	Spermidine	$C_7H_{19}N_3$	C00315	Arginine and proline metabolism
14	147.0532	L-Glutamate	$C_5H_9NO_4$	C00302	Alanine, aspartate and glutamate metabolism
15	148.0524	tans-Cinnamate	$C_9H_8O_2$	C00423	Phenylalanine metabolism
16	149.051	L-Methionine	$C_5H_{11}NO_2S$	C00073	Cysteine and methionine metabolism
17	152.0334	Xanthine	$C_5H_4N_4O_2$	C00385	Purine metabolism
18	161.1052	L-Carnitine	$C_7H_{15}NO_3$	C00318	Bile secretion
19	165.079	L-Phenylalanine	$C_9H_{11}NO_2$	C00079	Phenylalanine metabolism
20	173.0147	Sulfanilic acid	$C_6H_7NO_3S$	C06335	
21	161.0841	Tryptophol	$C_{10}H_{11}NO$	C00955	Tryptophan metabolism
22	184.0233	5-Hydroxyisourate	$C_5H_4N_4O_4$	C11821	Purine metabolism
23	204.0899	L-Tryptophan	$C_{11}H_{12}N_2O_2$	C00078	Tryptophan metabolism
24	208.0848	Kynurenine	$C_{10}H_{12}N_2O_3$	C01718	Tryptophan metabolism
25	229.0885	Ergothioneine	$C_9H_{15}N_3O_2S$	C05570	Histidine metabolism
26	243.0855	Cytidine	$C_9H_{13}N_3O_5$	C00475	Pyrimidine metabolism
27	257.1028	Glycerophosphocholine	$C_8H_{20}NO_6P$	C00670	Glycerophospholipid metabolism
28	392.2927	Ursodeoxycholic acid	$C_{24}H_{40}O_4$	C07880	Secondary bile acid biosynthesis
ESI-					
1	97.9769	Phosphate	H_3O_4P	C00009	Parathyroid hormone synthesis, secretion and action
2	102.0317	2-Oxobutanoate	$C_4H_6O_3$	C00109	Glycine, serine and threonine metabolism
3	103.0633	Acetoacetate	$C_4H_9NO_2$	C00164	Tyrosine metabolism
4	105.0426	L-Serine	$C_3H_7NO_3$	C00740	Glycine, serine and threonine metabolism
5	106.0266	Glycerate	$C_3H_6O_4$	C00258	Glycine, serine and threonine metabolism
6	118.0266	Succinate	$C_4H_6O_4$	C00042	Citrate cycle (TCA cycle)
7	122.0368	2-Hydroxybenzaldehyde	$C_7H_6O_2$	C06202	Biosynthesis of phenylpropanoids
8	129.0426	4-Oxoproline	$C_5H_7NO_3$	C01877	Arginine and proline metabolism

9	134.0215	Maleate	$C_4H_6O_5$	C00497	Butanoate metabolism
10	136.0372	2,3,4-Trihydroxybutanoic acid	$C_4H_8O_5$	C01620	Ascorbate and aldarate metabolism
11	141.0191	O-Phosphoethanolamine	$C_2H_8NO_4P$	C00346	Glycerophospholipid metabolism
12	146.0691	L-Glutamine	$C_5H_{10}N_2O_3$	C00064	Purine metabolism
13	161.9042	Trichloroacetic acid	$C_2HCl_3O_2$	C11150	Metabolism of xenobiotics by cytochrome P450
14	165.079	5-(3-Pyridyl)-2-hydroxy tetrahydrofuran	$C_9H_{11}NO_2$	C19578	Metabolism of xenobiotics by cytochrome P450
15	167.0219	Quinolinate	$C_7H_5NO_4$	C03722	Tryptophan metabolism
16	168.0283	Uric acid	$C_5H_4N_4O_3$	C00366	Purine metabolism
17	172.0137	Phosphorylcholine	$C_3H_9O_6P$	C00093	Glycerolipid metabolism
18	174.1117	L-Arginine	$C_6H_{14}N_4O_2$	C00062	Arginine and proline metabolism
19	175.0481	N-Acetyl-L-aspartic acid	$C_6H_9NO_5$	C01042	Alanine, aspartate and glutamate metabolism
20	181.0739	L-Tyrosine	$C_9H_{11}NO_3$	C00082	Tyrosine metabolism
21	192.027	Citrate	$C_6H_8O_7$	C00158	Citrate cycle (TCA cycle)
22	219.1107	Pantothenic acid	$C_9H_{17}NO_5$	C00864	beta-Alanine metabolism
23	244.0695	Uridine	$C_9H_{12}N_2O_6$	C00299	Pyrimidine metabolism
24	268.0808	Inosine	$C_{10}H_{12}N_4O_5$	C00294	Purine metabolism
25	280.2402	Linoleate	$C_{18}H_{32}O_2$	C01595	Linoleic acid metabolism
26	282.2559	Oleic acid	$C_{18}H_{34}O_2$	C00712	Fatty acid biosynthesis
27	274.178	9(S)-HODE	$C_{14}H_{26}O_5$	C14767	Linoleic acid metabolism
28	301.0563	N-acetyl-alpha-D-galactosamine 1-phosphate	$C_8H_{16}NO_9P$	C18060	Amino sugar and nucleotide sugar metabolism
29	304.2402	Arachidonate	$C_{20}H_{32}O_2$	C00219	Arachidonic acid metabolism
30	306.2559	Dihomo-gama-linolenic acid	$C_{20}H_{34}O_2$	C03242	Linoleic acid metabolism
31	307.0838	Glutathione	$C_{10}H_{17}N_3O_6S$	C00051	Glutathione metabolism
32	316.2038	4-Hydroxyretinoic acid	$C_{20}H_{28}O_3$	C16677	Retinol metabolism
33	320.2351	15H-11, 12-EETA	$C_{20}H_{32}O_3$	C14781	Arachidonic acid metabolism
34	334.2144	Prostaglandin A2	$C_{20}H_{30}O_4$	C05953	Arachidonic acid metabolism
35	465.309	Glycocholic acid	$C_{26}H_{43}NO_6$	C01921	Bile secretion
36	515.2917	Taurocholate	$C_{26}H_{45}NO_7S$	C05122	Bile secretion

Table S 5 Information of potential biomarkers in kidney sample

Mode	Accurate Mass (m/z)	Proposed Identify	Formula	KEEEG ID	Metabolic pathways
ESI+					
1	104.1075	Choline	$C_5H_{14}NO$	C00114	Glycine, serine and threonine metabolism
2	105.0426	L-Serine	$C_3H_7NO_3$	C00740	Glycine, serine and threonine metabolism
3	111.0433	Cytosine	$C_4H_5N_3O$	C00380	Pyrimidine metabolism
4	113.0589	Creatinine	$C_4H_7N_3O$	C00791	Arginine and proline metabolism
5	115.0633	L-Proline	$C_5H_9NO_2$	C00148	Arginine and proline metabolism

6	118.0868	Betaine	$C_5H_{12}NO_2$	C00719	Glycine, serine and threonine metabolism
7	119.0582	L-Homoserine	$C_4H_9NO_3$	C00263	Glycine, serine and threonine metabolism
8	121.0891	Phenylethylaoe	$C_8H_{11}N$	C02505	Phenylalanine metabolism
9	122.048	Niacinamide	$C_6H_6N_2O$	C00153	Nicotinate and nicotinamide metabolism
10	129.0426	Pyroglutamic acid	$C_5H_7NO_3$	C01879	Glutathione metabolism
11	131.0695	Creatine	$C_4H_9N_3O_2$	C00300	Arginine and proline metabolism
12	131.0946	L-Leucine	$C_6H_{13}NO_2$	C01570	2-Oxocarboxylic acid metabolism
13	132.0535	L-Asparagine	$C_4H_8N_2O_3$	C00152	Alanine, aspartate and glutamate metabolism
14	133.0375	L-Aspartic acid	$C_4H_7NO_4$	C00402	Alanine, aspartate and glutamate metabolism
15	134.0215	Malic acid	$C_4H_6O_5$	C00149	Citrate cycle (TCA cycle)
16	135.0684	2-Phenylacetamide	C_8H_9NO	C02505	Phenylalanine metabolism
17	136.0385	Hypoxanthine	$C_5H_4N_4O$	C00262	Purine metabolism
18	117.079	5-Aminopentanoate	$C_5H_{11}NO_2$	C00431	Arginine and proline metabolism
19	145.1579	Spermidine	$C_7H_{19}N_3$	C00315	Arginine and proline metabolism
20	268.0551	L-Homocystine	$C_8H_{16}N_2O_4S_2$	C01817	Cysteine and methionine metabolism
21	146.1181	Acetylcholine	$C_7H_{16}NO_2$	C01996	Bile secretion//Glycerophospholipid metabolism
22	146.1055	L-Lysine	$C_6H_{14}N_2O_2$	C00047	2-Oxocarboxylic acid metabolism
23	146.0691	L-Glutamine	$C_5H_{10}N_2O_3$	C00064	Purine metabolism
24	146.0844	Dimethylbenzimidazole	$C_9H_{10}N_2$	C03114	Riboflavin metabolism
25	148.0524	trans-Cinnamate	$C_9H_8O_2$	C00423	Phenylalanine metabolism
26	149.051	L-Methionine	$C_5H_{11}NO_2S$	C00073	Cysteine and methionine metabolism
27	150.0528	L-Xylulose	$C_5H_{10}O_5$	C00310	Ascorbate and aldarate metabolism
28	152.0334	Xanthine	$C_5H_4N_4O_2$	C00385	Purine metabolism
29	155.0695	L-Histidine	$C_6H_9N_3O_2$	C00135	Histidine metabolism
30	161.1052	L-Carnitine	$C_7H_{15}NO_3$	C00318	Bile secretion
31	165.079	L-Phenylalanine	$C_9H_{11}NO_2$	C00079	Phenylalanine metabolism
32	167.0582	Isopyridoxal	$C_8H_9NO_3$	C06051	Vita0 B6 metabolism
33	174.1117	Arginine	$C_6H_{14}N_4O_2$	C02385	Arginine and proline metabolism
34	188.1161	N6-Acetyl-L-lysine	$C_8H_{16}N_2O_3$	C02727	Lysine degradation
35	192.027	Citrate	$C_6H_8O_7$	C00158	Citrate cycle (TCA cycle)
36	193.0252	Phosphocreatinine	$C_4H_8N_3O_4P$		
37	179.0582	Hippuric acid	$C_9H_9NO_3$	C01586	Phenylalanine metabolism
38	204.0899	Tryptophan	$C_{11}H_{12}N_2O_2$	C00078	Tryptophan metabolism
39	257.1028	Glycerophosphocholine	$C_8H_{20}NO_6P$	C00670	Glycerophospholipid metabolism
40	267.0968	Deoxyguanosine	$C_{10}H_{13}N_5O_4$	C00330	Purine metabolism
41	515.2917	Taurallocholic acid	$C_{26}H_{45}NO_7S$	C00245	Taurine and hypotaurine metabolism
42	280.2402	Octadecadienoate	$C_{18}H_{32}O_2$	C01595	Linoleic acid metabolism
43	283.0917	Guanosine	$C_{10}H_{13}N_5O_5$	C00387	Purine metabolism
44	285.1365	Morphine	$C_{17}H_{19}NO_3$	C01516	Neuroactive ligand-receptor interaction
45	297.0896	5'-Methylthioadenosine	$C_{11}H_{15}N_5O_3S$	C00170	Cysteine and methionine metabolism
46	299.2824	3-Dehydrosphinganine	$C_{18}H_{37}NO_2$	C02934	Sphingolipid metabolism
47	301.2981	Sphinganine	$C_{18}H_{39}NO_2$	C00836	Sphingolipid metabolism
48	317.293	Phytosphingosine	$C_{18}H_{39}NO_3$	C12144	Sphingolipid metabolism
49	362.2093	Cortisol	$C_{21}H_{30}O_5$	C00735	Bile secretion

50	381.2644	Sphinganine 1-phosphate	$C_{18}H_{40}NO_5P$	C01120	Sphingolipid metabolism
51	399.3349	Palmitoylcarnitine	$C_{23}H_{45}NO_4$	C02990	Fatty acid metabolism
ESI-					
1	112.0273	Uracil	$C_4H_4N_2O_2$	C00106	Pyrimidine metabolism
2	117.0578	Indole	C_8H_7N	C00463	Tryptophan metabolism
3	118.0266	Succinate	$C_4H_6O_4$	C00042	Citrate cycle (TCA cycle)
4	119.0582	Threonine	$C_4H_9NO_3$	C00300	Glycine, serine and threonine metabolism
5	125.0147	Taurine	$C_2H_7NO_3S$	C00245	Taurine and hypotaurine metabolism
6	136.0372	2,3,4-Trihydroxybutanoic acid	$C_4H_8O_5$	C01620	Ascorbate and aldarate metabolism
7	147.0532	L-Glutamate	$C_5H_9NO_4$	C00025	Alanine, aspartate and glutamate metabolism
8	176.0321	Ascorbate	$C_6H_8O_6$		Glutathione metabolism
9	180.0634	L-Tagatose	$C_6H_{12}O_6$	C00795	Galactose metabolism
10	181.0739	L-Tyrosine	$C_9H_{11}NO_3$	C00082	Tyrosine metabolism
11	268.0808	Inosine	$C_{10}H_{12}N_4O_5$	C00294	Purine metabolism
12	282.2559	Oleic acid	$C_{18}H_{34}O_2$	C00712	Fatty acid biosynthesis
13	302.2246	Retinyl ester	$C_{20}H_{30}O_2$	C02075	Retinol metabolism
14	304.2402	Arachidonic acid	$C_{20}H_{32}O_2$	C00219	Arachidonic acid metabolism
15	408.2876	Bile acid	$C_{24}H_{40}O_5$	C01558	Fat digestion and absorption
16	153.079	Dopamine	$C_8H_{11}NO_2$	C03758	Tyrosine metabolism