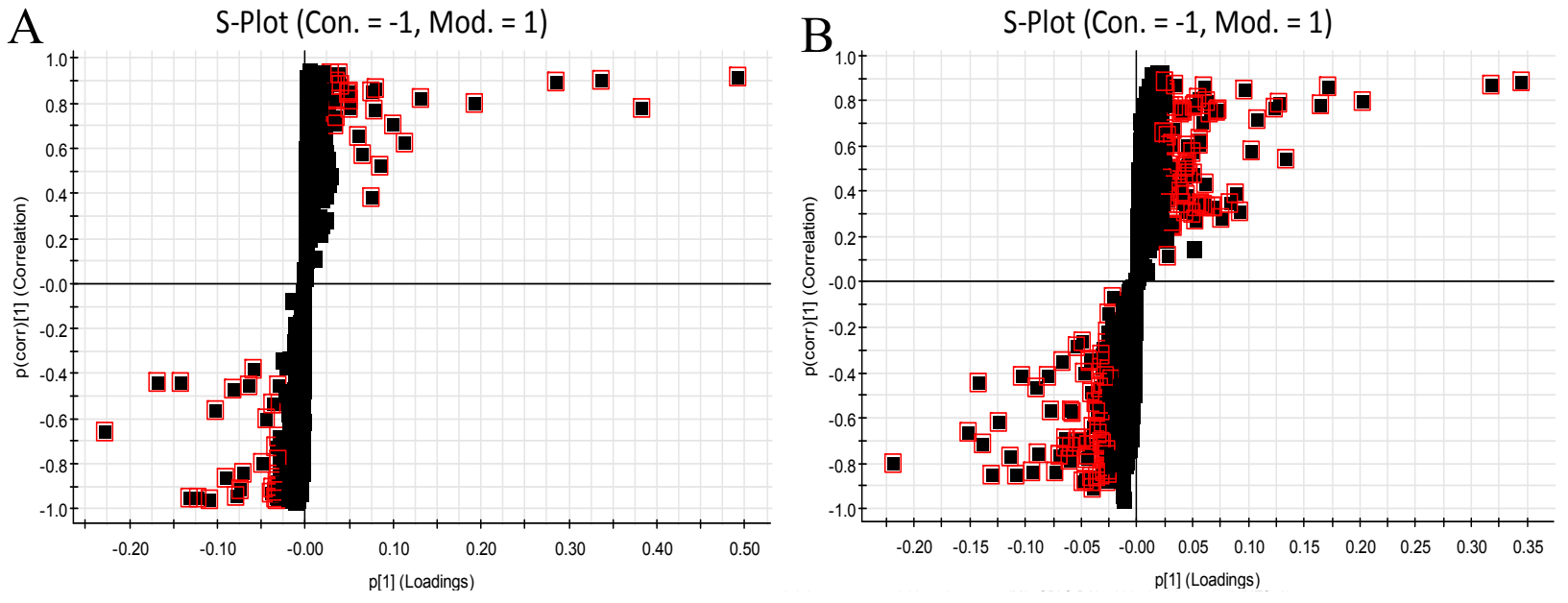
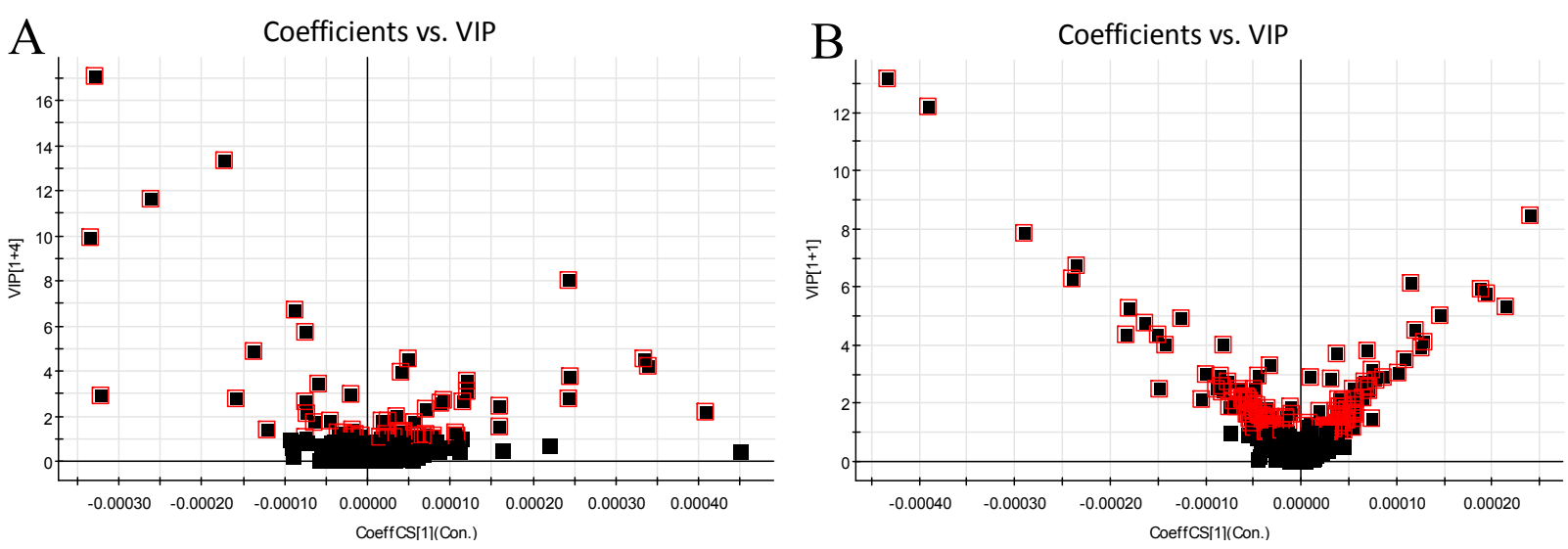
Electronic Supplementary Material (ESI) for RSC Advances.



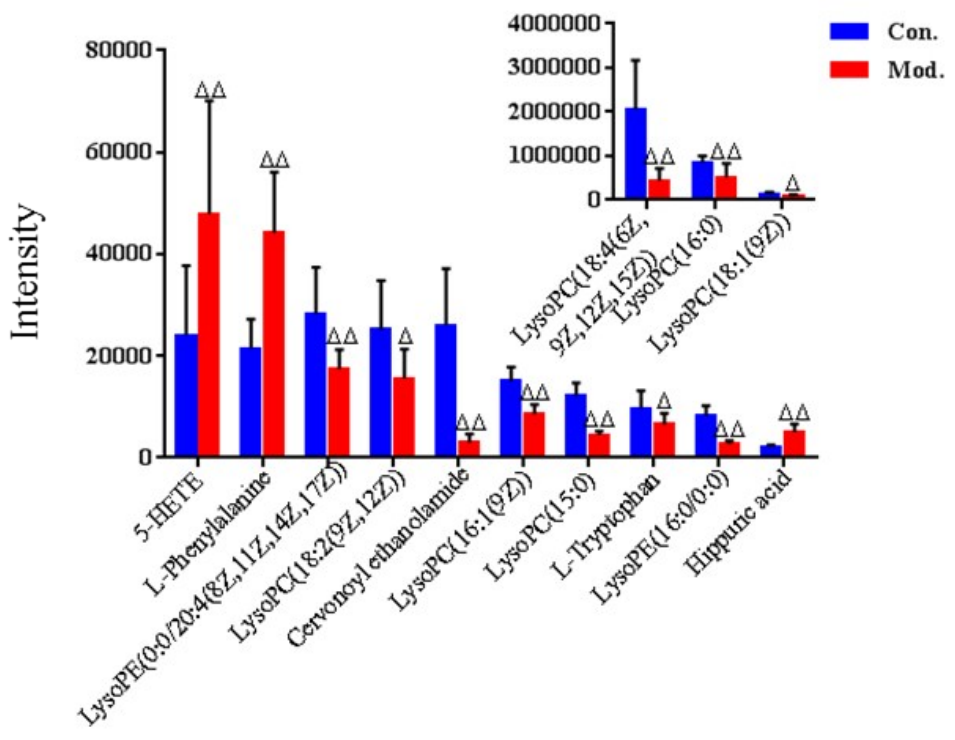
Supplementary Figure 1 S-plot of serum profile of control group and model group scanned by positive ion mode and negative ion mode. (OPLS-DA).

Note: A:In the positive ion mode, B: In the negative ion mode; Con: the sham group, Mod: the model group



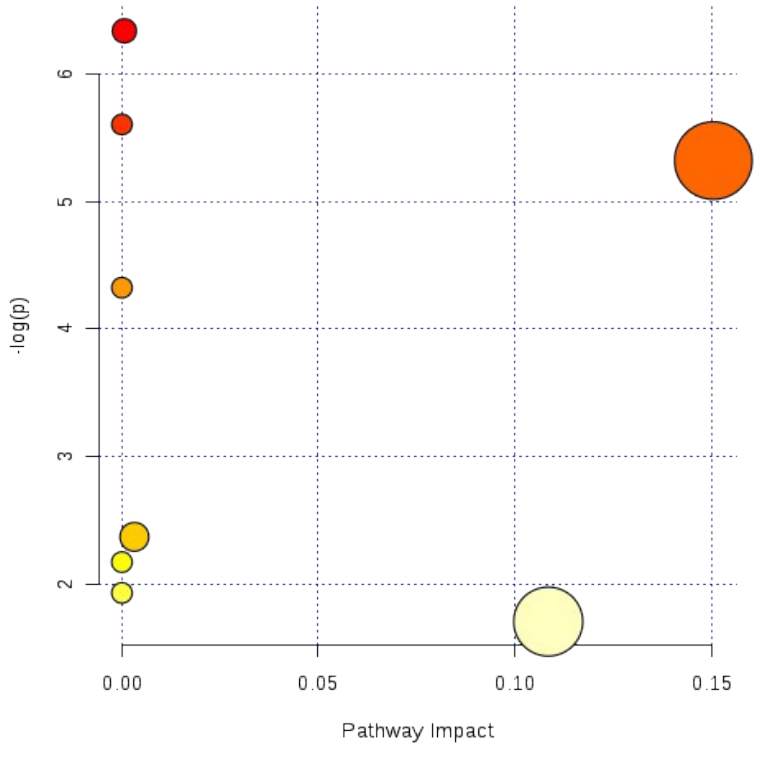
Supplementary Figure 2 VIP-plot of serum profile of control group and model group scanned by positive ion mode and negative ion mode. (OPLS-DA)

Note: A:In the positive ion mode, B: In the negative ion mode; Con: the sham group, Mod: the model group

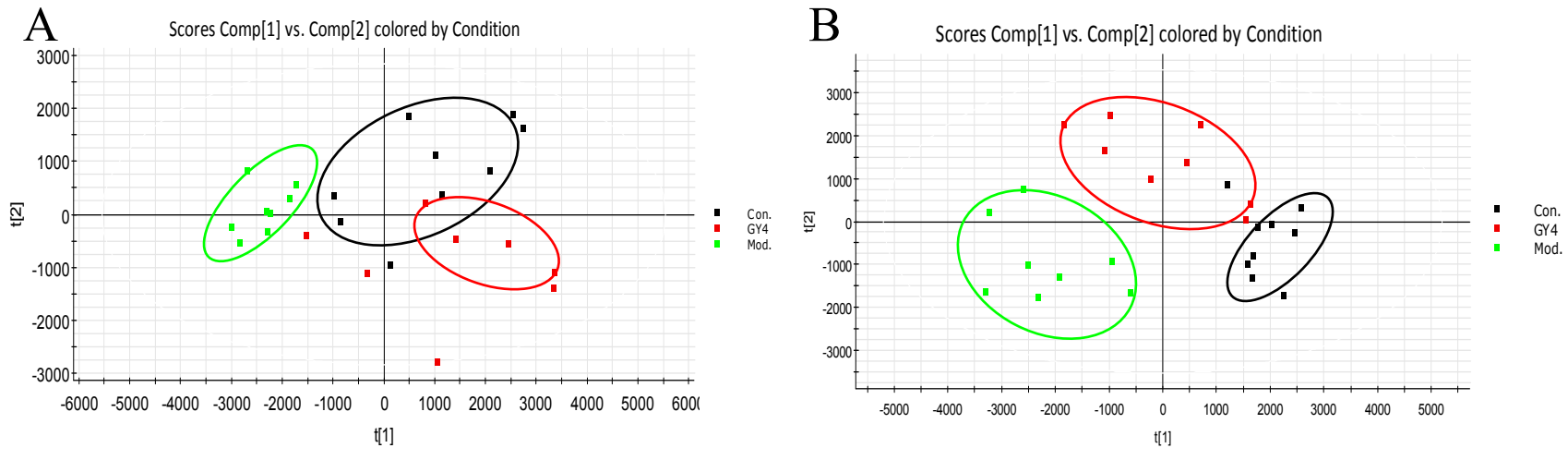


Supplementary Figure 3 Content changes of potential biomarkers in ECB model serum by positive ion mode.

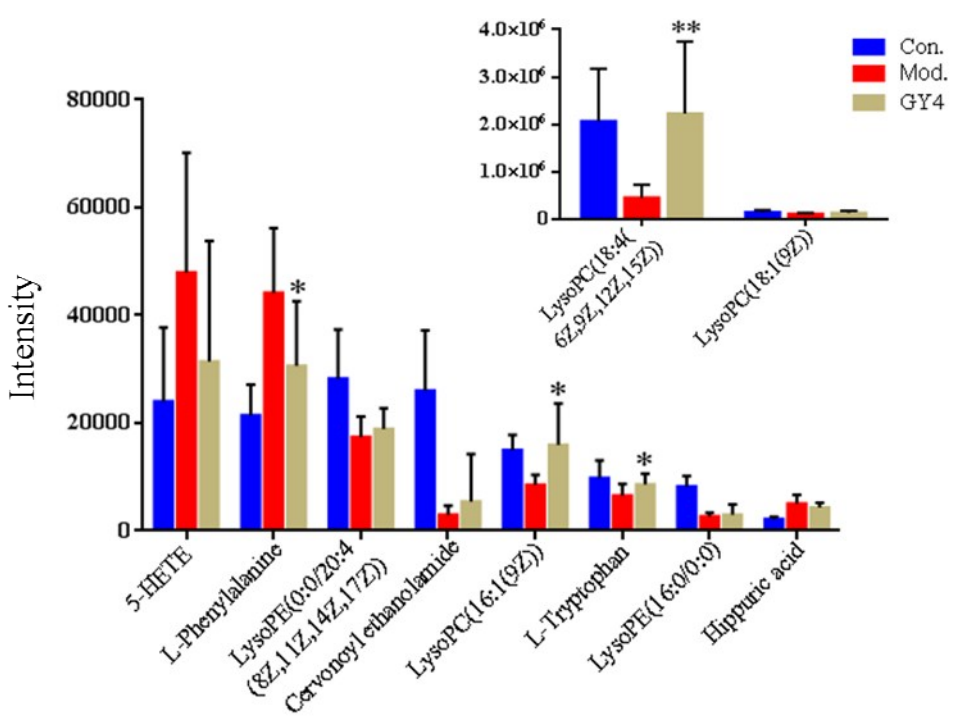
Note: △P<0.05, △△P<0.01, compared with control group. Con: the sham group, Mod: the model group.



Supplementary Figure 4 Summary of network pathway analysis with MetPA software
1: Phenylalanine, tyrosine and tryptophan biosynthesis; 2: Phenylalanine metabolism; 3: Tryptophan metabolism; 4: Glycerophospholipid metabolism; 5: Arachidonic acid metabolism; 6: Aminoacyl-tRNA biosynthesis.



Supplementary Figure 5 Score plot of serum profile after oral administration of PF scanned by positive ion mode (A) and negative ion mode (B). (Data were analyzed by PLS-DA).
Con: the sham group, Mod: the model group, GY4: the PF group



Supplementary Figure 6 Content changes of potential biomarkers of the rats in PF group by positive ion mode.
Note: *P<0.05, **P<0.01, compared with the model group. Con: the sham group, Mod: the model group, GY4: the PF group.

Supplementary Table 1 MS/MS information of biomarkers in positive and negative ion mode.

No.	Rt (min)	Actual Mass	[M-H]-/[M+H]+	Proposed Composition	PostulatedIdentity	MS/MS fragment ion (m/z)
1	1.36	165.0789	$[M+H]^+$	$C_9H_{11}NO_2$	L-Phenylalanine	166.0869$[M+H]^+$ 151.0489$[M+H-NH]^+$ 120.0823$[M+H-CH_2O_2]^+$
2	1.73	204.0898	[M-H]-	C11H12N2O2	L-Tryptophan	203.08327[M-H]- 188.9841[M-H-H2N]- 160.0454[M-H-CHO2]- 130.0694[M-H-C2H5NO2]- 116.0563[M-H-C3H7NO2]-
3	2.20	179.0582	[M-H]-	C9H9NO3	Hippuric acid	178.0504[M-H]- 162.0572[M-H-O]- 136.0478[M-H-CO2]- 121.1302[M-H-C2HO2]-
4	4.79	515.3011	[M-H]-	C26H46NO7P	LysoPC(18:4(6Z,9Z,12Z,15Z))	514.293[M-H]- 425.2906[M-H-C3H7NO2]- 407.2827[M-H-C7H7O]- 331.1941[M-H-C6H18NO3P]-
5	5.51	372.2664	[M+H]+	C24H36O3	Cervonoyl ethanolamide	373.2745[M+H]+ 319.2409[M+H-C4H6]+ 184.0763[M+H-C14H21]+ 147.1204[M+H-C13H22O3]+
6	7.25	493.3168	[M+H]+	C24H48NO7P	LysoPC(16:1(9Z))	494.3242[M+H]+ 311.2596[M+H-C5H14NO4P]+ 258.1153[M+H-C13H34NO2]+ 184.0742[M+H-C19H36NO2]+
7	7.54	519.3324	[M+H]+	C26H50NO7P	LysoPC(18:2(9Z,12Z))	520.34[M+H]+ 483.2494[M+H-H5O2]+ 337.2709[M+H-C5H14NO4P]+ 303.0184[M+H-C13H31NO]+ 184.0740[M+H-C21H38NO2]+
8	7.71	501.2855	[M-H]-	C25H44NO7P	LysoPE(0:0/20:4(8Z,11Z,14Z,17Z))	500.279[M-H]- 325.2380[M-H-C6H10NO3P]- 279.2303[M-H-C7H12NO5P]- 224.0699[M-H-C18H28O2]-
9	8.13	453.2855	[M+H]+	C21H44NO7P	LysoPE(16:0/0:0)	454.2939[M+H]+ 362.2845[M+H-C2H6NO3]+ 282.2861[M+H-C2H7NO6P]+ 184.0746[M+H-C16H32NO2]+
10	8.23	495.3324	[M+H]+	C24H50NO7P	LysoPC(16:0)	496.3404[M+H]+ 478.3301[M+H-H2O]+ 313.2761[M+H-C5H14NO4P]+ 258.1119[M+H-C10H25NO3P]+ 184.0699[M+H-C14H35NO4P]+
11	8.64	521.3481	[M+H]+	C26H52NO7P	LysoPC(18:1(9Z))	522.3563[M+H]+ 480.3441[M+H-C3H6]+ 339.2904[M+H-C6H18NO3P]+ 258.1117[M+H-C14H34NO3]+ 184.0680[M+H-C16H37NO4P]+
12	8.99	320.2351	[M-H]-	C20H32O3	5-HETE	319.2278[M-H]- 269.2482[M-H-CH6O2]- 222.0830[M-H-C7H13]- 179.1047[M-H-C9H16O]-
13	9.61	481.3168	[M+H]+	C23H48NO7P	LysoPC(15:0)	428.0325[M+H]+ 361.2827[M+H-C5H13O3]+ 184.0758[M+H-C13H33NO4P]+ 135.0766[M+H-C19H41NO4]+

Supplementary Table 2 Result from ingenuity pathway analysis with Metaboanalyst.

No.	Pathway name	Total	Expected	Hits	Raw p	Impact
1	Phenylalanine, tyrosine and tryptophan biosynthesis	4	0.01712	1	0.01703	0.5
2	Phenylalanine metabolism	9	0.03852	1	0.03797	0.40741
3	Tryptophan metabolism	41	0.17546	1	0.1634	0.15684
4	Glycerophospholipid metabolism	30	0.12839	1	0.12192	0.04444
5	Arachidonic acid metabolism	36	0.15407	1	0.14475	0
6	Aminoacyl-tRNA biosynthesis	67	0.28673	2	0.02980	0

Note: Total: The total number of compound in the pathway; Hits: The number of accurate matching markers in the upload data; Raw p: Original P values obtained by pathway analysis; Impact: The affected value of pathways obtained by topological analysis.

Supplementary Table 3 Trend of serum potential biomarkers after oral administration of PF

No.	Rt min	Actual Mass	Proposed Composition	Postulated Identity	Trend in ECB	PF
1	1.36	165.0789	$C_9H_{11}NO_2$	L-Phenylalanine	$\uparrow^{\triangle\triangle}$	+*
2	1.73	204.0898	$C_{11}H_{12}N_2O_2$	L-Tryptophan	$\downarrow^{\triangle}$	+*
3	2.20	179.0582	$C_9H_9NO_3$	Hippuric acid	$\uparrow^{\triangle\triangle}$	+
4	4.79	515.3011	$C_{26}H_{46}NO_7P$	LysoPC(18:4(6Z,9Z,12Z,15Z))	$\downarrow^{\triangle\triangle}$	+**
5	5.51	372.2664	$C_{24}H_{36}O_3$	Cervonoyl ethanolamide	$\downarrow^{\triangle\triangle}$	+
6	7.25	493.3168	$C_{24}H_{48}NO_7P$	LysoPC(16:1(9Z))	$\downarrow^{\triangle\triangle}$	+*
7	7.54	519.3324	$C_{26}H_{50}NO_7P$	LysoPC(18:2(9Z,12Z))	$\downarrow^{\triangle}$	-
8	7.71	501.2855	$C_{25}H_{44}NO_7P$	LysoPE(0:0/20:4(8Z,11Z,14Z,17Z))	$\downarrow^{\triangle\triangle}$	+
9	8.13	453.2855	$C_{21}H_{44}NO_7P$	LysoPE(16:0/0:0)	$\downarrow^{\triangle\triangle}$	+
10	8.23	495.3324	$C_{24}H_{50}NO_7P$	LysoPC(16:0)	$\downarrow^{\triangle\triangle}$	-
11	8.64	521.3481	$C_{26}H_{52}NO_7P$	LysoPC(18:1(9Z))	$\downarrow^{\triangle}$	+
12	8.99	320.2351	$C_{20}H_{32}O_3$	5-HETE	$\uparrow^{\triangle\triangle}$	+
13	9.61	481.3168	$C_{23}H_{48}NO_7P$	LysoPC(15:0)	$\downarrow^{\triangle\triangle}$	-

Note : ↑↓ indicates that the level of the marker is increased or decreased in the urine of rats in the ECB model group ;+&- indicates that the drug has no or no effect on the marker's recall; Compared with the control group, $^{\triangle}P<0.05$, $^{\triangle\triangle}P<0.01$; Compared with the model group, *P<0.05, ** P<0.01.