SUPPLEMENTARY INFORMATION

Metabolomic analysis of urethane-induced lung carcinogenesis in rats and the ameliorative effect of Qi-Yu-San-Long decoction

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Table caption

Table S1 Chromatography and mass spectrometry parameters.

Table S2 Potential discriminatory biomarkers in plasma and lung tissues of rats in the control, model and QYSLD groups detected by UPLC-Q-TOF/MS.

Figure caption

Figure S1 Representative BPIs of rat plasma samples of control (A, D), model (B, E) and QYSLD groups (C, F) acquired in the ESI$^+$ and ESI$^-$ mode by UPLC-Q-TOF/MS; Representative BPIs of rats lung tissue samples of control (G, J), model (H, K) and QYSLD groups (I, L) acquired in the ESI$^+$ and ESI$^-$ mode by UPLC-Q-TOF/MS.

Figure S2 Lung OPLS-DA score plots and their corresponding S-plots in dual ESI ion mode of the control group and model group (ESI$^+$ mode: (A, B) (R^2Y=95%, Q^2 =93%, p[CV-ANOVA]=1.20×10^{-6}); ESI$^-$ mode: (E, F) (R^2Y=72%, Q^2 =62%, p[CV-ANOVA]=1.39×10^{-2})). Lung OPLS-DA score plots and their corresponding S-plots in dual ESI ion mode of the model group and QYSLD group (ESI$^+$ mode: (C, D) (R^2Y=75%, Q^2 =65%, p[CV-ANOVA]=5.81×10^{-3}); ESI$^-$ mode: (G, H) (R^2Y=45%, Q^2 =41%, p[CV-ANOVA]=2.9×10^{-2})).

Figure S3 Permutation test plots of plasma samples in ESI$^+$ mode (A) and ESI$^-$ mode (C) for the control and model groups; permutation test plots of plasma samples in ESI$^+$ mode (B) and ESI$^-$ mode (D) for

the model and QYSLD groups. Permutation test plots of lung tissue samples in ESI$^+$ mode (E) and ESI$^-$ mode (G) for the control and model groups; permutation test plots of lung tissue samples in ESI$^+$ mode (F) and ESI$^-$ mode (H) for the model and QYSLD groups.

Table S1 Chromatography and mass spectrometry parameters.

Chromatography						
Column temperature	Injection volume	Flow rate	Chromatographic column	Mobile phases	Mobile phase gradient elution procedure	
40 °C	2 μL	0.2 mL·min^{-1}	BEH C$_{18}$ column (100 mm×2.1 mm, 1.7 μm)	A: 0.1% v/v formic acid in water B: acetonitrile	0-4 min, 92%−60% A; 4-19 min, 60%−15% A; 19-24 min, 15%−5% A; 24-27 min, 5%−92% A; 27-30 min, 92% A	
Mass spectrometry						
Ion source temperature	Scanning range	Capillary voltage	Voltage of cone	Gas flow of the cone	Desolvation temperature	Gas flow rate	Collision energy
120 °C	*m/z*: 50−1200 Da	ESI$^+$: 3.0 KV; ESI$^-$: 2.5 KV	40 V	40 L·h^{-1}	400 °C	600 L·h^{-1}	low collision energy: 6 V; high collision energy: 15∼40V

Table S2 Potential discriminatory biomarkers in plasma and lung tissues of rats in the control, model and QYSLD groups detected by UPLC-Q-TOF/MS.

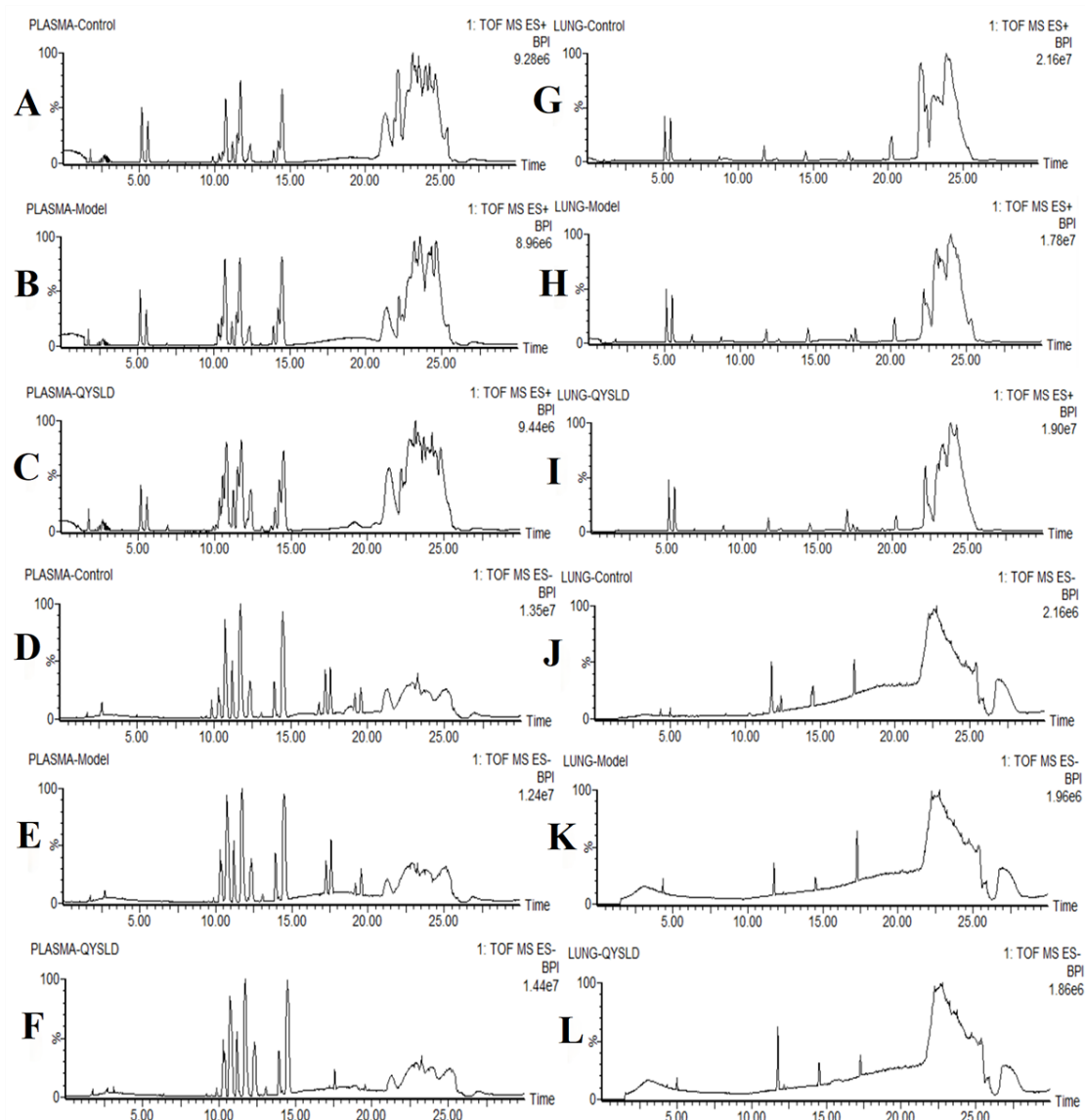| Metabolite	*m/z*	T$_R$	Possible MS/MS	FC		VIP		Trend		source
				M VS. C	Q VS. M	M VS. C	Q VS. M	M VS. C	Q VS. M	
unknow	447.2518	13.78	283.2629	4.06	1.40	3.84	3.94	↑	↓	Plasma（ESI⁻）
unknow	706.8040	23.02	361.2717	1.59	0.52	3.67	3.70	↑	↓	Lung（ESI⁺）
unknow	572.3001	10.71	258.1089	1.80	0.74	2.11	1.02	↑	↓	Plasma（ESI⁺）
unknow	666.3116	14.91	648.2903	2.26	0.71	1.83	1.87	↑	↓	Plasma（ESI⁻）
unknow	763.5887	25.00	282.0514	0.66	1.67	1.22	1.01	↓	↑	Plasma（ESI⁺）

C: Control, M: Model, Q: QYSLD

Figure S1 Representative BPIs of rat plasma samples of control (A, D), model (B, E) and QYSLD groups (C, F) acquired in the ESI$^+$ and ESI$^-$ mode by UPLC-Q-TOF/MS; Representative BPIs of rats lung tissue samples of control (G, J), model (H, K) and QYSLD groups (I, L) acquired in the ESI$^+$ and ESI$^-$ mode by UPLC-Q-TOF/MS.
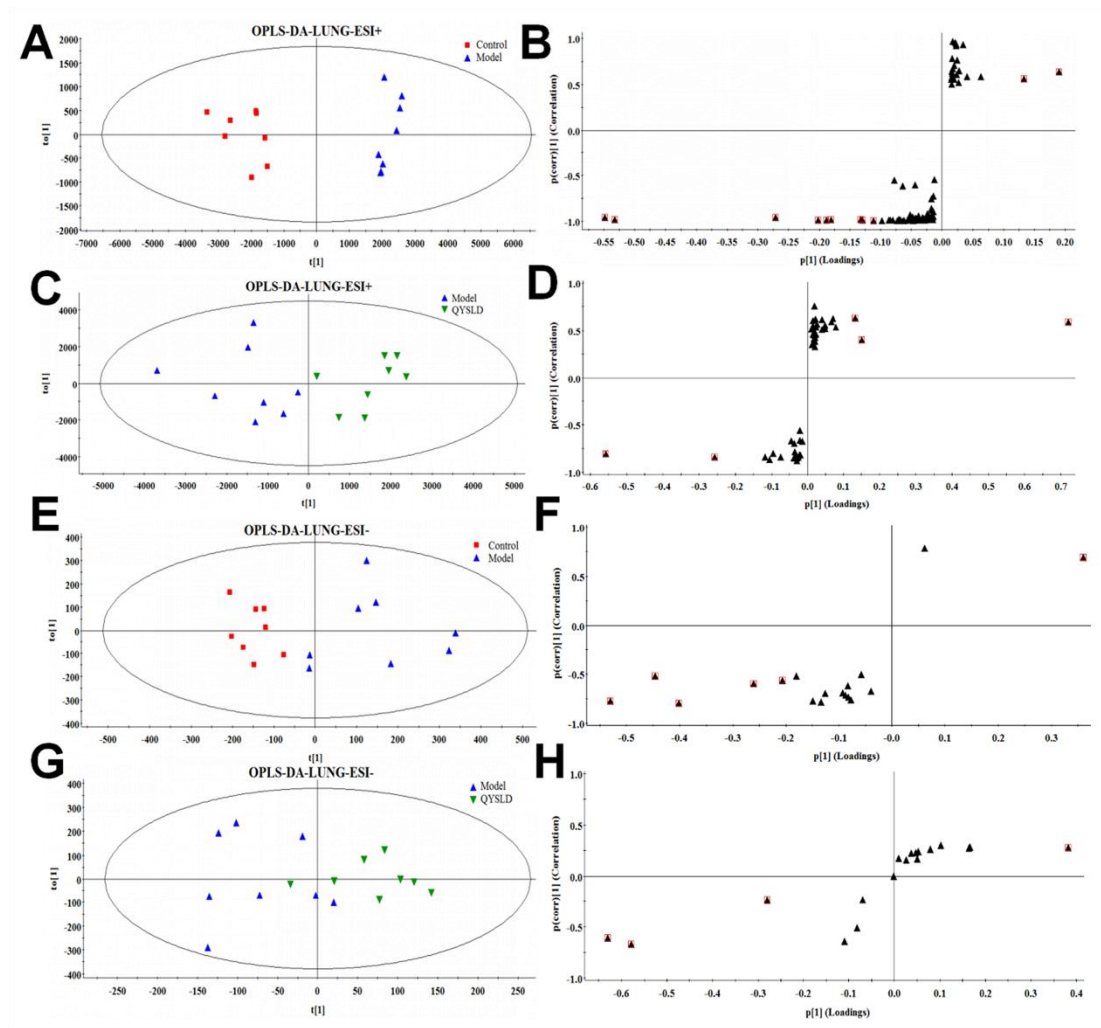
Figure S2 Lung OPLS-DA score plots and their corresponding S-plots in dual ESI ion mode of the control group and model group (ESI$^+$ mode: (A, B) (R^2Y=95%, Q^2 =93%, p[CV-ANOVA]=1.20×10^{-6}); ESI$^-$ mode: (E, F) (R^2Y=72%, Q^2 =62%, p[CV-ANOVA]=1.39×10^{-2})). Lung OPLS-DA score plots and their corresponding S-plots in dual ESI ion mode of the model group and QYSLD group (ESI$^+$ mode: (C, D) (R^2Y=75%, Q^2 =65%, p[CV-ANOVA]=5.81×10^{-3}); ESI$^-$ mode: (G, H) (R^2Y=45%, Q^2 =41%, p[CV-ANOVA]=2.9×10^{-2})).
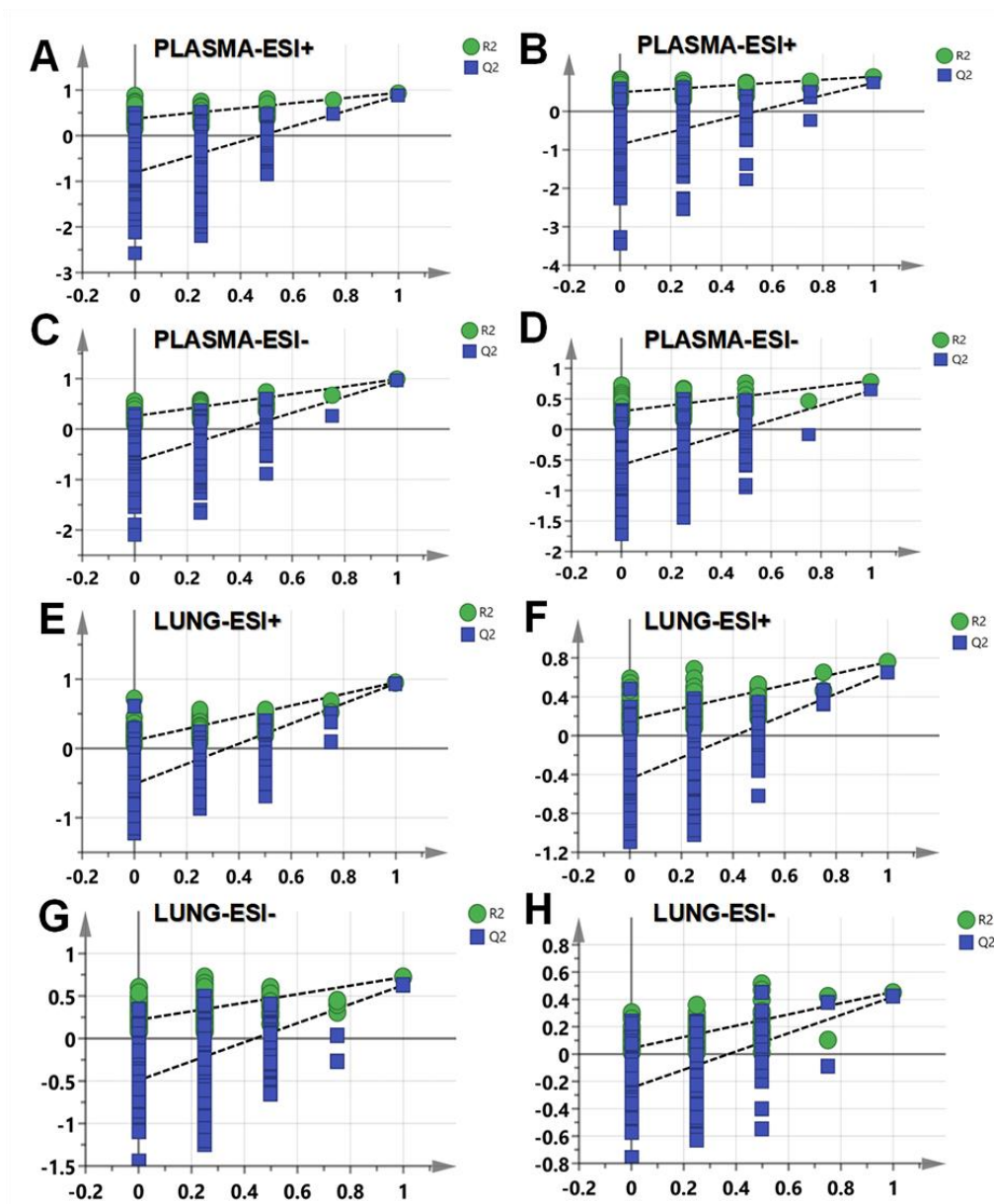
Figure S3 Permutation test plots of plasma samples in ESI⁺ mode (A) and ESI⁻ mode (C) for the control and model groups; permutation test plots of plasma samples in ESI⁺ mode (B) and ESI⁻ mode (D) for the model and QYSLD groups. Permutation test plots of lung tissue samples in ESI⁺ mode (E) and ESI⁻ mode (G) for the control and model groups; permutation test plots of lung tissue samples in ESI⁺ mode (F) and ESI⁻ mode (H) for the model and QYSLD groups.