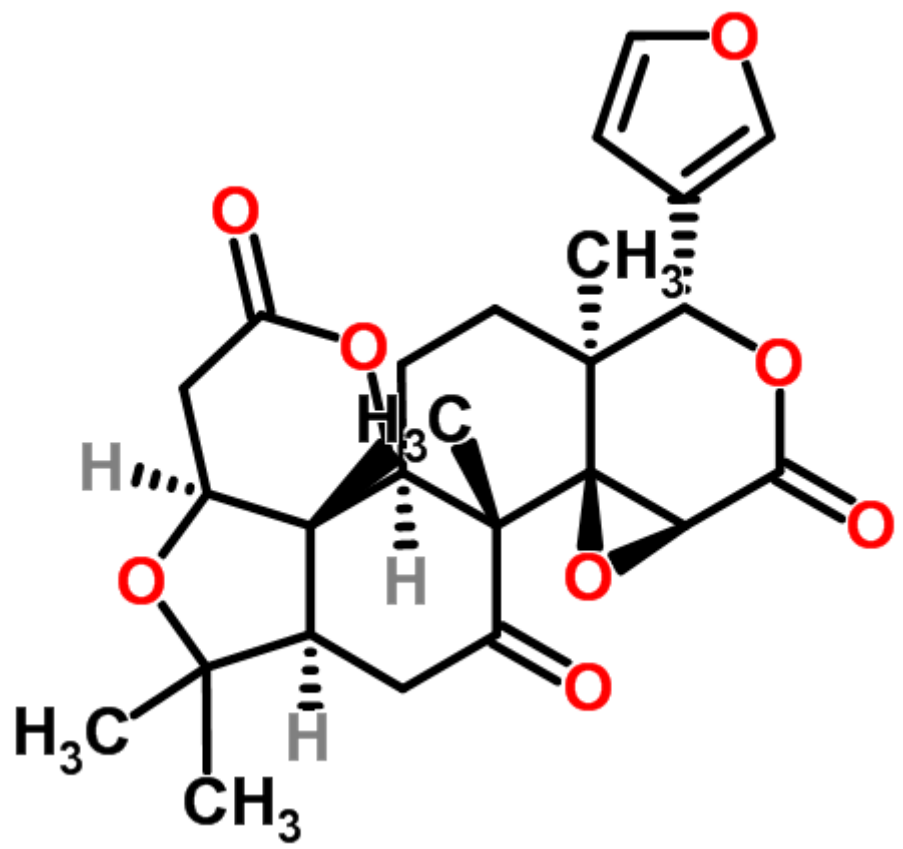

Fig.S1. Chemical structure of Limonin.

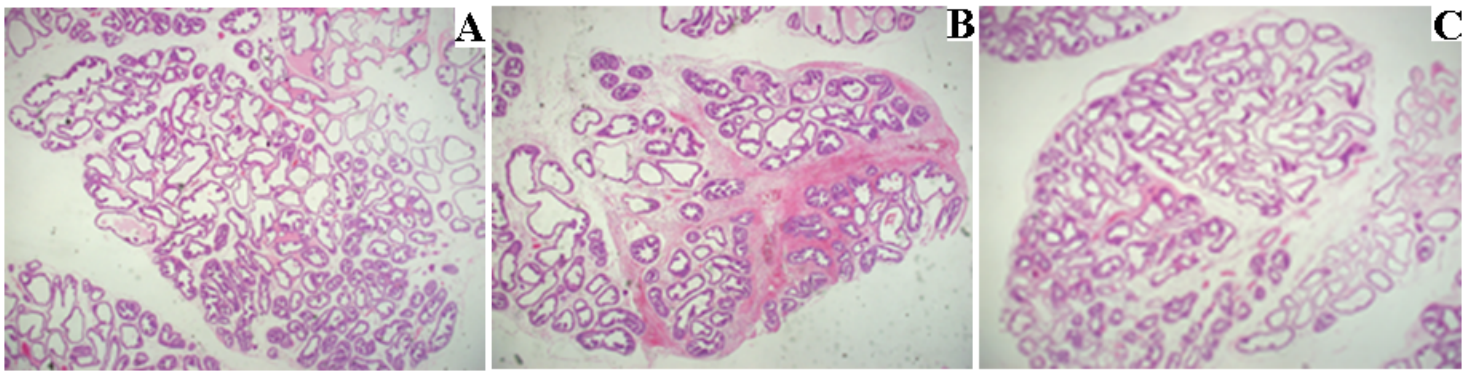

Fig. S2. **Representative photomicrographs of tissue sections stained with H&E**. (A) Control group; (B) model group; (C) limonin group. (Magnification, 20×).

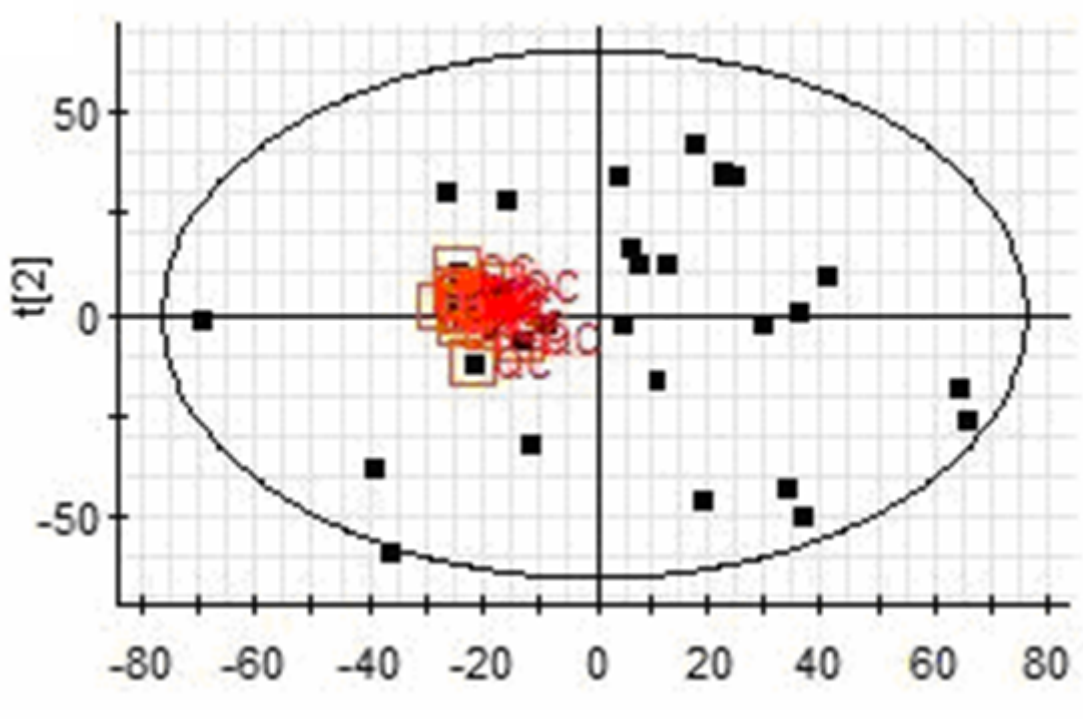

Fig. S3. Data overview and quality assurance when using principle component analysis (PCA) that demonstrates good method reproducibility in overall test carried out with UPLC-Q-TOF/MS. Black box present urine samples, and samples in red box present QC.

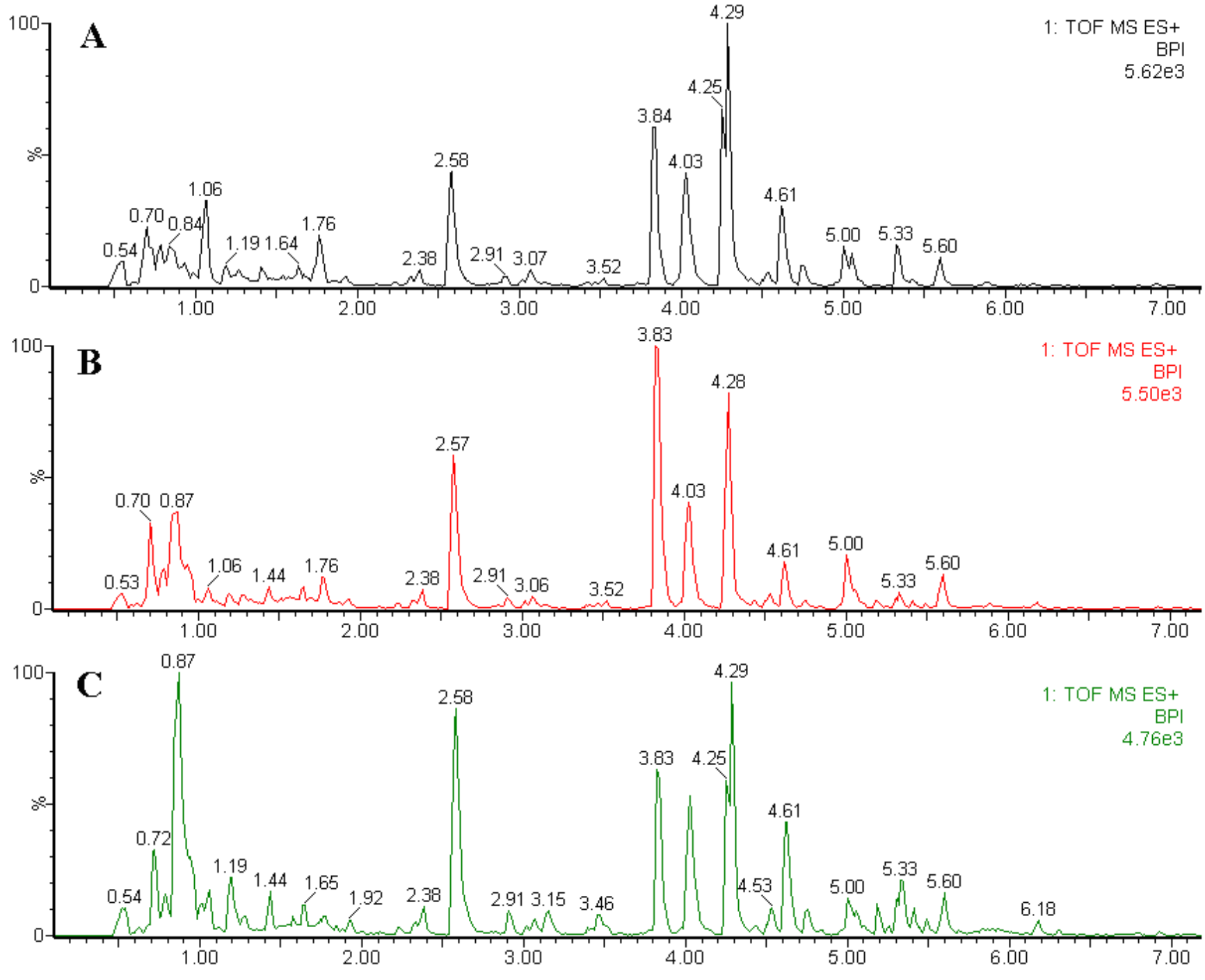

Fig. S4 UPLC-Q-TOF/HDMS Based Peak Intensity (BPI) chromatograms of urine samples from each groups.

(A) control group; (B) model group; (C) limonin treatment group.

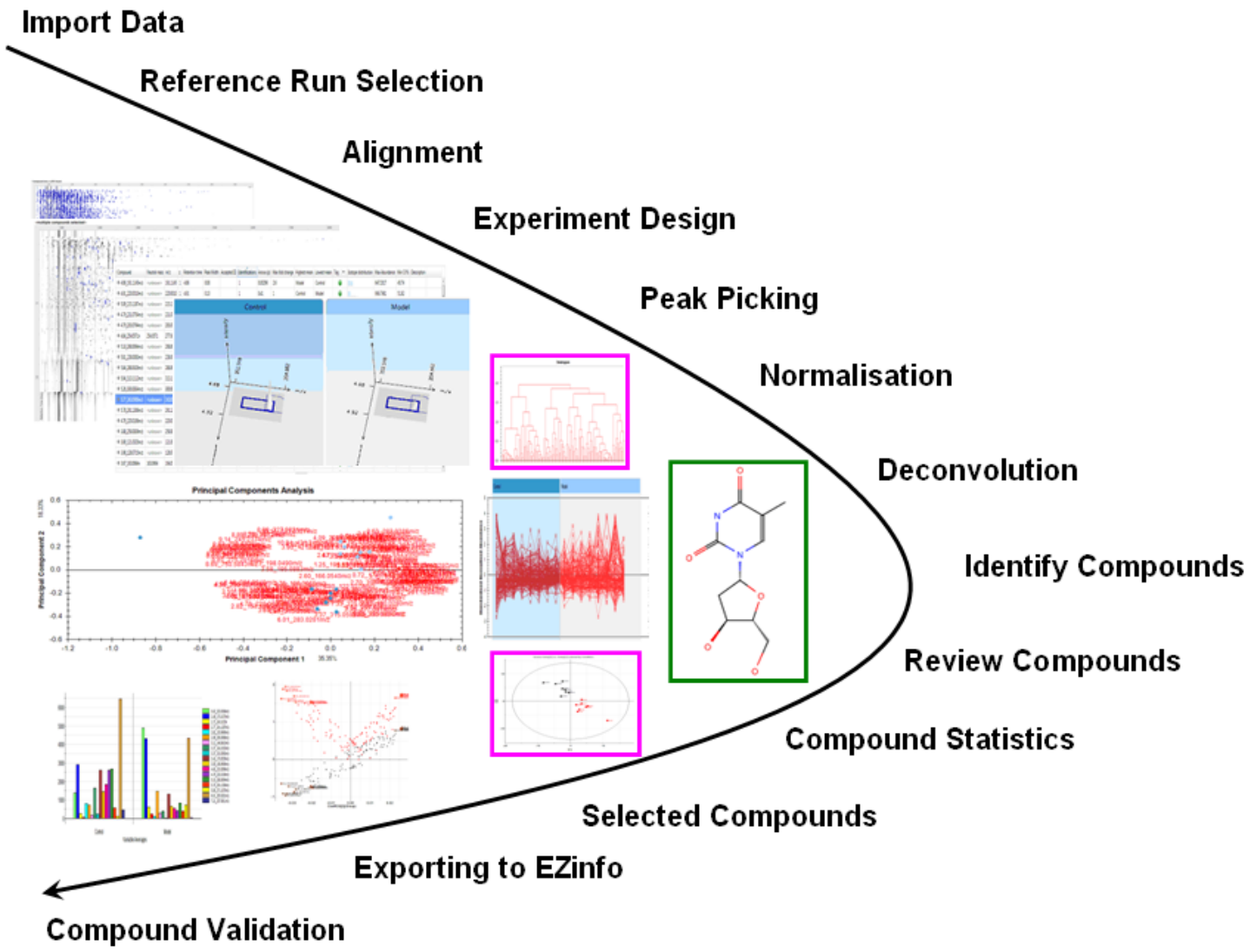

Fig. S5 Detailed analysis workflow of TransOmics informatics for metabolomics data from large biological data sets

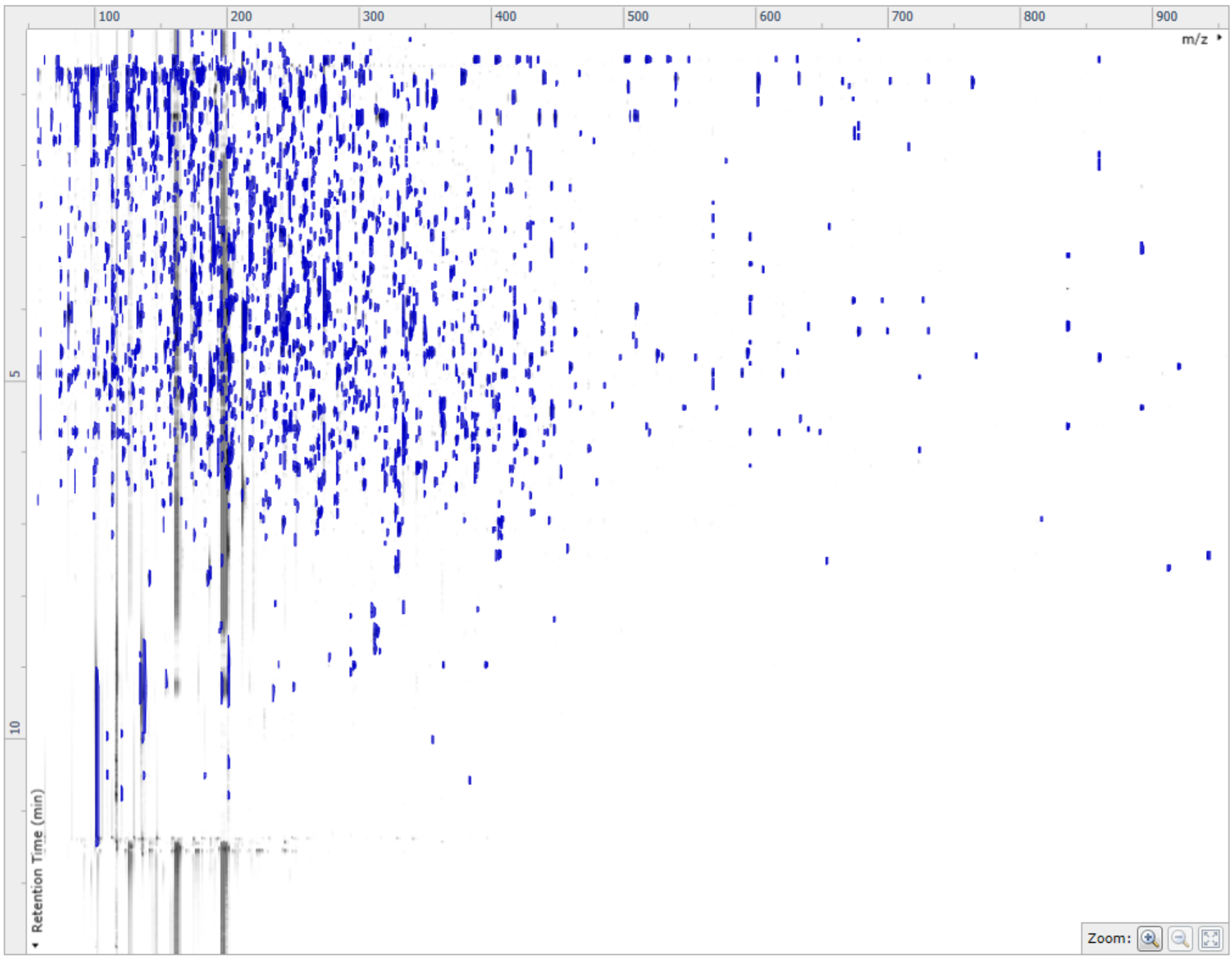

Fig. S6 Typical 2D ion intensity map taking a detailed approach to alignment. The map return to after having generated the Alignment vectors automatically. The Alignment algorithm will generate ‘compound ions’ in the retention time direction. The ‘compound ions’ will be highlighted in blue.

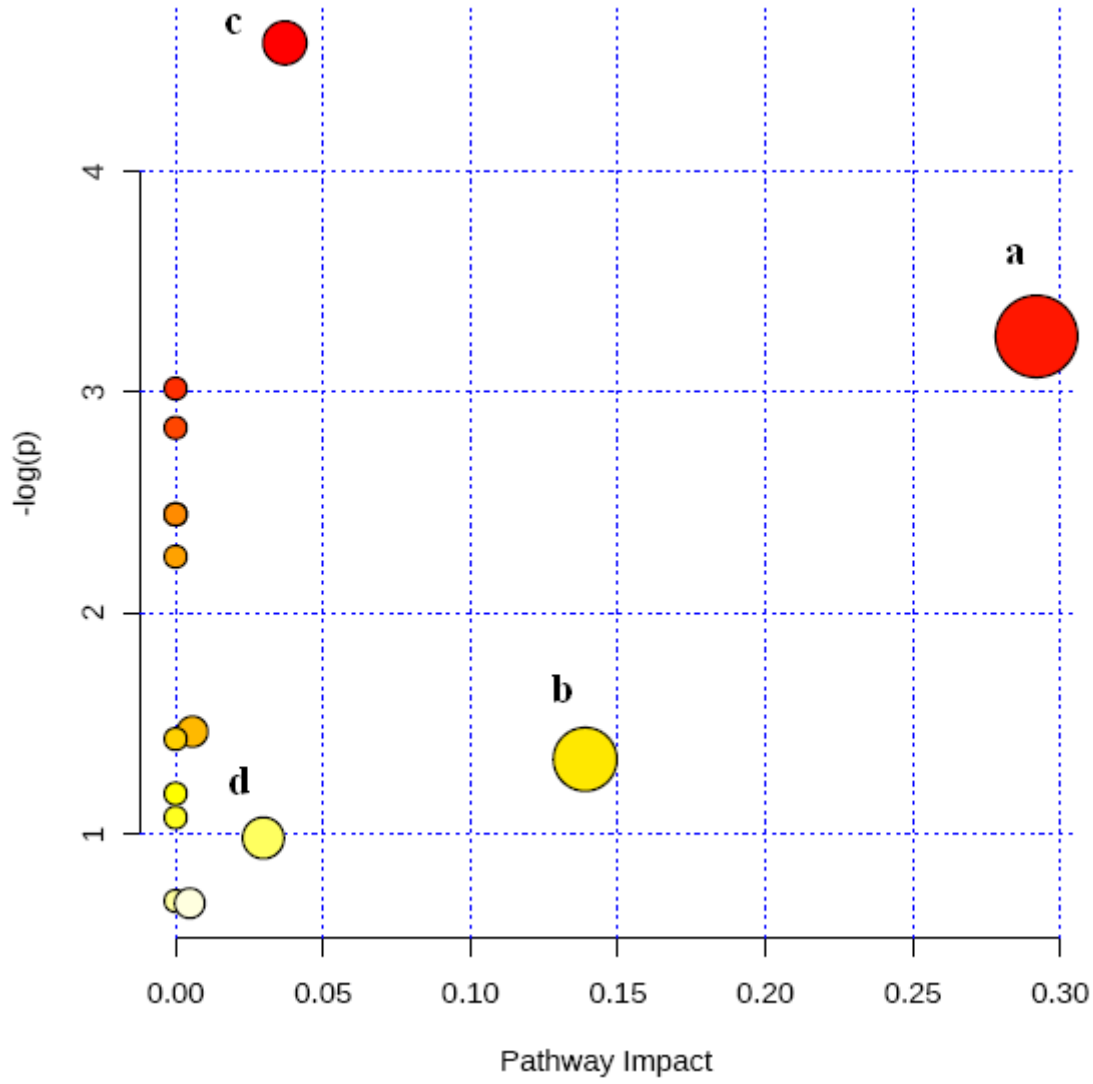

Fig. S7 Summary of pathway analysis with MetPA tool

a, Glycine, serine and threonine metabolism; b, Glycerophospholipid metabolism; c, Glyoxylate and dicarboxylate metabolism; d, Primary bile acid biosynthesis

Table S1. Expressions of TNF-α and concentration of protein extravasation in all the groups.

Group	Plasma protein extravasation	TNF-α
Control (Sham)	20.61±2.72	1.37±0.29
Model	31.50±8.67*	3.46±0.73**
Limonin	21.83±2.23#	1.40±0.48##

Note:
* significant difference from control at $p < 0.05$.
** Significant difference from control at $p < 0.001$.
# Significant difference from model at $p < 0.05$.
Significant difference from model at $p < 0.001$.

Table S2. The result of stability of the proposed method in urine metabolomics

Mode	m/z	Retention Time(min)		Mass accuracy		Peak area	
		Mean	CV(%)	Mean	CV(%)	Mean	CV(%)
ESI-	124.0068	1.06	0	124.0069	0.000377	62.224	2.748375
	312.1077	1.216	0.45043	312.1085	0.00015	40.68	5.516837
	173.0810	5.168	0.086535	173.0799	0.000378	179.1556	2.80058
	407.2794	6.942	0.064421	407.2792	0.000169	130.9644	5.364034

Table. S3. Information of potential biomarkers related with NBP identified in negative ion mode.

No	Rt	m/z	Compound ID	Adducts	Formula	Mass Error (ppm)	Compound	Trend	VIP
1	7.51	653.2589	HMDB00890	M-H	$C_{36}H_{38}N_4O_8$	-3.48	Uroporphyrin IV	↑	14.754
2	4.09	178.0506	HMDB00714	M-H	$C_9H_9NO_3$	1.20	Hippuric acid	↑	14.7333
3	3.53	74.0239	HMDB00123	M-H	$C_2H_5NO_2$	-4.31	Glycine	↓	8.75318
4	3.30	258.0278	HMDB00592	M-H	$C_6H_{13}NO_8S$	-2.20	Glucosamine 6-sulfate	↓	8.45604
5	5.47	313.0913	HMDB02357	M-H	$C_{10}H_{21}NO_8P$	-4.24	Lecithin	↓	7.31511
6	5.80	144.1026	HMDB06831	M-H	$C_7H_{15}NO_2$	1.11	3-Dehydroxycarnitine	↓	7.15925
7	5.38	375.1289	HMDB00244	M-H	$C_{17}H_{20}N_4O_6$	-4.24	Riboflavin	↓	6.9626
8	5.35	199.0970	HMDB00603	M-H	$C_{10}H_{16}O_4$	0.05	Decenedioic acid	↓	5.97479
9	5.23	206.0808	HMDB00512	M-H	$C_{11}H_{13}NO_3$	-4.50	N-Acetyl-L-phenylalanine	↑	4.66216
10	5.15	72.9925	HMDB00119	M-H	$C_2H_2O_3$	-0.62	Glyoxylic acid	↓	4.55963
11	6.30	363.2157	HMDB00903	M-H	$C_{21}H_{32}O_5$	-4.10	Tetrahydrocortisone	↑	4.22078
12	2.13	251.0778	HMDB00071	M-H	$C_{10}H_{12}N_4O_4$	-0.98	Deoxyinosine	↑	3.79514
13	2.35	117.0551	HMDB02011	M-H	$C_5H_{10}O_3$	-0.33	4-Hydroxyisovaleric acid	↓	3.6648
14	2.31	149.0445	HMDB00366	M-H	$C_5H_{10}O_5$	-3.30	2-Deoxyribonic acid	↑	3.60094
15	5.71	75.0080	HMDB00115	M-H	$C_2H_4O_3$	-2.48	Glycolic acid	↓	3.57737
16	3.83	201.1121	HMDB00792	M-H	$C_{10}H_{18}O_4$	-3.08	Sebacic acid	↑	3.47617
17	5.94	193.0341	HMDB02545	M-H	$C_6H_{10}O_7$	-3.75	Galacturonic acid	↑	3.35138
18	1.44	212.0017	HMDB00682	M-H	$C_8H_7NO_4S$	-0.40	Indoxyl sulfate	↓	3.34021
19	5.42	186.0546	HMDB00734	M-H	$C_{11}H_9NO_2$	-4.89	Indoleacrylic acid	↓	3.30703
20	1.24	338.0907	HMDB05034	M-H	$C_{12}H_{21}NO_8S$	-0.72	Topiramate	↓	3.28156

Table S4. Result from ingenuity pathway analysis with Metabolyst based on KEGG.

No	Pathway	Total	Expected	Hits	Raw p	Impact
1	Glyoxylate and dicarboxylate metabolism	16	0.15977	2	0.010263	0.03
2	Glycine, serine and threonine metabolism	32	0.31954	2	0.038719	0.29
2	Linoleic acid metabolism	5	0.049929	1	0.04901	0
3	Cyanoamino acid metabolism	6	0.059914	1	0.05854	0
4	alpha-Linolenic acid metabolism	9	0.089872	1	0.086602	0
5	Methane metabolism	9	0.089872	1	0.086602	0
6	Nitrogen metabolism	9	0.089872	1	0.086602	0
7	Riboflavin metabolism	11	0.10984	1	0.10488	0
8	Glutathione metabolism	26	0.25963	1	0.23149	0
9	Porphyrin and chlorophyll metabolism	27	0.26961	1	0.23931	0
10	Glycerophospholipid metabolism	30	0.29957	1	0.26233	0.14
11	Arachidonic acid metabolism	36	0.35949	1	0.30643	0
12	Tryptophan metabolism	41	0.40942	1	0.3413	0
13	Primary bile acid biosynthesis	46	0.45934	1	0.37454	0.03
14	Aminoacyl-tRNA biosynthesis	67	0.66904	1	0.49784	0
15	Purine metabolism	68	0.67903	1	0.50311	0.00