

Table.S1 The gradient program for urine sample.

Time (min)	Flow rate (mL·min ⁻¹)	Solvent A (%)	Solvent B (%)	Curve
Initial	0.4	1	99	6
4	0.4	14	86	6
8	0.4	42	58	6
9	0.4	100	0	6
10	0.4	100	0	6
11	0.4	1	99	6
12	0.4	1	99	6

Table.S2 Urine potential biomarkers identified in positive and negative mode

NO.	Rt min	M/Z Determined	M/Z Calculate d	Scan Mode	Proposed Composition	Postulated Identity	Change Trend
1	0.61	195.0510	195.0510	ESI-	C ₆ H ₁₂ O ₇	Galactonic acid	↓
2	0.62	177.0400	177.0400	ESI-	C ₆ H ₁₀ O ₆	3-Keto-b-D-galactose	↓
3	0.68	300.0395	300.0395	ESI-	C ₈ H ₁₅ NO ₉ S	N-Acetylgalactosamine 4-sulphate	↓
4	0.87	170.0928	170.0928	ESI+	C ₇ H ₁₁ N ₃ O ₂	1-Methylhistidine	↓
5	1.13	138.0919	138.0919	ESI+	C ₈ H ₁₁ NO	2-Hydroxyphenethylamine	↑
6	1.14	121.0654	121.0654	ESI+	C ₈ H ₈ O	Phenylacetaldehyde	↑
7	1.23	191.0195	191.0195	ESI-	C ₆ H ₈ O ₇	2,3-Diketo-L-gulonate	↑
8	1.37	282.1208	282.1208	ESI+	C ₁₁ H ₁₅ N ₅ O ₄	2'-O-Methyladenosine	↑
9	1.43	231.0979	231.0979	ESI-	C ₉ H ₁₆ N ₂ O ₅	4-butanoate	↓
10	1.51	314.1226	314.1226	ESI+	C ₁₄ H ₁₉ NO ₇	Tyramine glucuronide	↑
11	1.94	330.0611	330.0611	ESI+	C ₁₀ H ₁₂ N ₅ O ₆ P	Adenosine2',3'-cyclic phosphate	↑
12	1.99	166.0504	166.0504	ESI+	C ₈ H ₇ NO ₃	4-Pyridoxolactone	↓
13	2.0	346.0558	346.0558	ESI+	C ₁₀ H ₁₂ N ₅ O ₇ P	Guanosine2',3'-cyclic phosphate	↑
14	2.20	130.0867	130.0867	ESI+	C ₆ H ₁₁ NO ₂	Pipecolic acid	↑
15	2.34	189.1239	189.1239	ESI+	C ₈ H ₁₆ N ₂ O ₃	Glycyl-L-leucine	↑
16	2.47	168.0659	168.0659	ESI+	C ₈ H ₉ NO ₃	Pyridoxal	↑
17	2.75	209.0929	209.0929	ESI+	C ₁₀ H ₁₂ N ₂ O ₃	Formyl-5-hydroxykynurenamine	↓
18	3.21	197.0450	197.0450	ESI-	C ₉ H ₁₀ O ₅	3-(3,4-Dihydroxyphenyl)lactic acid	↑
19	3.45	194.0450	194.0450	ESI-	C ₉ H ₉ NO ₄	Dopaquinone	↑
20	3.57	181.0497	181.0497	ESI-	C ₉ H ₁₀ O ₄	3-Methoxy-4-hydroxyphenylglycol aldehyde	↑
21	3.92	180.0657	180.0657	ESI-	C ₉ H ₁₁ NO ₃	Beta-Tyrosine	↑
22	3.95	182.0819	182.0819	ESI+	C ₉ H ₁₁ NO ₃	L-Tyrosine	↑
23	4.26	179.0343	179.0343	ESI-	C ₉ H ₈ O ₄	3,4-Dihydroxy-trans-cinnamate	↑
24	4.38	165.0550	165.0550	ESI-	C ₉ H ₁₀ O ₃	Homovanillin	↑
25	4.48	167.0708	167.0708	ESI+	C ₉ H ₁₀ O ₃	D-Phenyllactic acid	↓
26	4.51	134.0615	134.0615	ESI-	C ₈ H ₉ NO	N-Acetylarylamine	↑
27	5.51	181.0494	181.0494	ESI+	C ₉ H ₈ O ₄	4-Hydroxyphenylpyruvic acid	↑
28	5.70	194.0453	194.0453	ESI-	C ₉ H ₉ NO ₄	Leucodopachrome	↑
29	5.76	181.0501	181.0501	ESI+	C ₉ H ₈ O ₄	2-Hydroxy-3-(4-hydroxyphenyl)propenoic acid	↓
30	5.91	167.0708	167.0708	ESI+	C ₉ H ₁₀ O ₃	Phenyllactic acid	↑
31	6.18	204.0658	204.0658	ESI-	C ₁₁ H ₁₁ NO ₃	Indolelactic acid	↑
32	7.77	193.0345	193.0345	ESI-	C ₆ H ₁₀ O ₇	3-Dehydro-L-gulonate	↓

Note: ↑↓It indicates that the level of urine in rats with Liver-fired Type hypertensive model is increased or decreased.

Table.S3 Secondary fragment Information of potential biomarkers in urine sample.

Rt min	Scan Mode	Actual-M	Postulated Identify	MS/MS fragmentation(m/z)
0.61	ESI-	195.0510	Galactonic acid	195.0510[M-H]-,147.0293[M-H-CH4O2]-,129.0188[M-H-CH6O3]-, 96.9926[M-H-C2H10O4]-, 75.0033[M-H-C4H8O4]-
0.62	ESI-	177.0400	3-Keto-b-D-galactose	177.0399[M-H]-,162.0528[M-H-O]-,143.0344[M-H-O-H2O2]-,131.0344[M-H-CH2O2]-, 125.0239[M-H-H4O3]-
0.68	ESI-	300.0395	N-Acetylgalactosamine 4-sulphate	300.0389[M-H]-,199.0276[M-H-C3H3NO3]-,181.0171[M-H-C3H5NO4]-,139.0269[M-H-C2H9O6S]-,101.0603[M-H-C3H5NO7S]-
0.87	ESI+	170.0928	1-Methylhistidine	170.0930[M+H]+,153.0902[M+H-HO]+,124.0875[M+H-CH2O2]+,116.0374[M+H-H8NO2]+, 109.0766[M+H-CH3NO2]+
1.13	ESI+	138.0919	2-Hydroxyphenethylamine	138.0919[M+H]+,122.0732[M+H-H2N]+,109.0653[M+H-CH3N]+
1.14	ESI+	121.0654	Phenylacetaldehyde	121.0653[M+H]+, 106.0782[M+H-O]+
1.23	ESI-	191.0195	2,3-Diketo-L-gulonate	173.0086[M-H]-,147.0293[M-H-CO2]-,129.0188[M-H-CH2O3]-,112.0160[M-H-CH3O4]-, 110.9718[M-H-C2H8O3]-
1.37	ESI+	282.1208	2'-O-Methyladenosine	282.1202[M+H]+,265.1175[M+H-HO]+,178.0729[M+H-C4H8O3]+,133.0388[M+H-C6H13O4]+,109.0514[M+H-C7H11NO4]+
1.43	ESI-	231.0979	4-butanoate	189.1239[M-H-CO2]-,171.0770[M-H-C2H4O2]-,153.0664[M-H-C2H6O3]-,145.0739[M-H-C3H4NO2]-,128.0348[M-H-C4H9NO2]-,126.0191[M-H-C4H11NO2]-, 82.0293[M-H-C5H11NO4]-
1.51	ESI+	314.1226	Tyramine glucuronide	314.1240[M+H]+,271.1182[M+H-CHNO]+,227.0919[M+H-C3H5NO2]+,210.0892[M+H-C3H6NO3]+,179.0708[M+H-C4H9NO4]+,151.0759[M+H-C5H9NO5]+, 121.0891[M+H-C6H9O7]+
1.94	ESI+	330.0611	Adenosine2',3'-cyclic phosphate	330.0603[M+H]+,312.0498[M+H-H2O]+,269.0314[M+H-C2H5O2]+,232.0834[M+H-H3O4P]+,204.0885[M+H-CH3O5P]+,177.0191[M+H-C5H5N4O2]+,151.0160[M+H-C6H5N5O2]+,119.9976[M+H-C7H8N5O3]+

1.99	ESI+	166.0504	4-Pyridoxolactone	166.0504[M+H] ⁺ ,148.0399[M+H-H ₂ O] ⁺ ,121.0528[M+H-CHO ₂] ⁺ ,109.0528[M+H-C ₂ H ₂ O ₂] ⁺
2.00	ESI+	346.0558	Guanosine2',3'-cyclic phosphate	346.0553[M+H] ⁺ ,330.0603[M+H-O] ⁺ ,266.0889[M+H-HO ₃ P] ⁺ ,230.0314[M+H-CH ₉ O ₄ P] ⁺ ,197.0100[M+H-CH ₁₂ NO ₅ P] ⁺ ,152.0698[M+H-C ₄ H ₅ NO ₆ P] ⁺ ,135.0671[M+H-C ₄ H ₆ NO ₇ P] ⁺ ,110.0480[M+H-C ₅ H ₇ N ₃ O ₆ P] ⁺
2.20	ESI+	130.0867	Pipecolic acid	130.0868[M+H] ⁺ , 114.0919[M+H-O] ⁺
2.34	ESI+	189.1239	Glycyl-L-leucine	172.1212[M+H-HO] ⁺ ,154.0868[M+H-H ₅ NO] ⁺ ,144.1025[M+H-CH ₃ NO] ⁺ ,120.0449[M+H-CH ₁₁ NO ₂] ⁺ ,101.1204[M+H-C ₂ H ₂ NO ₃] ⁺
2.47	ESI+	168.0659	Pyridoxal	168.0661[M+H] ⁺ ,153.0790[M+H-O] ⁺ ,126.0681[M+H-CNO] ⁺ ,104.0262[M+H-CH ₆ NO ₂] ⁺
2.75	ESI+	209.0928	Formyl-5-hydroxykynurenamine	209.0926[M+H] ⁺ ,192.0899[M+H-HO] ⁺ ,181.0977[M+H-CO] ⁺ ,166.0868[M+H-CHNO] ⁺ ,148.0762[M+H-CH ₃ NO ₂] ⁺ ,135.0684[M+H-C ₂ H ₄ NO ₂] ⁺ ,126.0344[M+H-CH ₉ NO ₃] ⁺
3.21	ESI-	197.0450	3-(3,4-Dihydroxyphenyl)lactic acid	197.0450[M-H] ⁻ ,182.0579[M-H-O] ⁻ ,167.0708[M-H-O ₂] ⁻ ,138.0681[M-H-CO ₃] ⁻ , 109.0290[M-H-C ₃ H ₄ O ₃] ⁻
3.45	ESI-	194.0450	Dopaquinone	194.0453[M-H] ⁻ ,151.0269[M-H-C ₂ H ₃ O] ⁻ ,123.0446[M-H-C ₂ HNO ₂] ⁻ , 121.0290[M-H-C ₂ H ₃ NO ₂] ⁻
3.57	ESI-	181.0498	3-Methoxy-4-hydroxyphenylglycol aldehyde	181.0501[M-H] ⁻ ,163.0395[M-H-H ₂ O] ⁻ ,135.0082[M-H-C ₂ H ₆ O] ⁻ ,119.0133[M-H-C ₂ H ₆ O ₂] ⁻ , 107.0133[M-H-C ₃ H ₆ O ₂] ⁻
3.92	ESI-	180.0657	Beta-Tyrosine	180.0661[M-H] ⁻ ,167.0708[M-H-N] ⁻ ,152.0837[M-H-NO] ⁻ ,137.0841[M-H-CO ₂] ⁻ , 108.0575[M-H-C ₂ H ₂ NO ₂] ⁻
3.93	ESI+	182.0819	L-Tyrosine	182.0817[M+H] ⁺ ,162.0555[M+H-H ₄ O] ⁺ ,138.0919[M+H-CO ₂] ⁺ ,117.0340[M+H-CH ₇ NO ₂] ⁺ , 109.0653[M+H-C ₂ H ₃ NO ₂] ⁺
4.26	ESI-	179.0343	3,4-Dihydroxy-trans-cinnamate	179.0344[M-H] ⁻ ,163.0395[M-H-O] ⁻ ,147.0446[M-H-O ₂] ⁻ ,135.0446[M-H-CO ₂] ⁻ , 121.0290[M-H-C ₂ H ₂ O ₂] ⁻
4.38	ESI-	165.0550	Homovanillin	165.0552[M-H] ⁻ ,150.0317[M-H-CH ₃] ⁻ ,139.0759[M-H-CO] ⁻ ,121.0290[M-H-C ₂ H ₄ O] ⁻ ,119.0133[M-H-C ₂ H ₆ O] ⁻
4.48	ESI+	167.0708	D-Phenyllactic acid	167.0708[M+H] ⁺ ,149.0603[M+H-

4.51	ESI-	134.0615	N-Acetylarylamine	H2O]+,130.0419[M+H-H5O2]+,121.0653[M+H-CH2O2]+, 107.0861[M+H-CO3]+ 134.0606[M-H]-,93.0578[M-H-C2HO]-,92.0500[M-H-C2H2O]-,77.0391[M-H-C2H3NO]-
5.51	ESI+	181.0494	4-Hydroxyphenylpyruvic acid	181.0501[M+H]+,163.0395[M+H-H2O]+,149.0603[M+H-O2]+,137.0603[M+H-CO2]+,135.0810[M+H-O3]+,105.0340[M+H-C2H4O3]+
5.70	ESI-	194.0453	Leucodopachrome	194.0453[M-H]-,179.0582[M-H-O]-,150.0555[M-H-CO2]-,121.0164[M-H-C3H5O2]-, 93.0340[M-H-C3H3NO3]-
5.76	ESI+	181.0500	2-Hydroxy-3-(4-hydroxyphenyl)propenoic acid	181.0501[M+H]+,164.0473[M+H-HO]+,135.0446[M+H-CH2O2]+,121.0653[M+H-CO3]+, 107.0497[M+H-C2H2O3]+
5.91	ESI+	167.0708	Phenyllactic acid	167.0708[M+H]+,151.0759[M+H-O]+,133.0653[M+H-H2O2]+,120.0939[M+H-O3]+, 107.0861[M+H-CO3]+
6.18	ESI-	204.0658	Indolelactic acid	204.0661[M-H]-,186.0555[M-H-H2O]-,158.0606[M-H-CH2O2]-, 130.0657[M-H-C2H2O3]-,116.0473[M-H-C6H2N]-
7.77	ESI-	193.0345	3-Dehydro-L-gulonate	179.0556[M-H-O]-,151.0606[M-H-CO2]-,130.9981[M-H-C2H6O2]-, 112.9875[M-H-C2H8O3]-, 100.9875[M-H-C3H8O3]-

Table.S4 Identification and change trends of the differential metabolites.

NO.	Postulated Identity	Y	L	Z	H
1	Galactonic acid	—	—	—	—
2	3-Keto-b-D-galactose	—	—	—	√
3	N-Acetylgalactosamine 4-sulphate	—	—	√	√
4	1-Methylhistidine	—	√	√	√
5	2-Hydroxyphenethylamine	√	√	√	√
6	Phenylacetaldehyde	√	√	√	√
7	2,3-Diketo-L-gulonate	—	—	—	—
8	2'-O-Methyladenosine	—	—	—	—
9	4-butanoate	—	—	—	—
10	Tyramine glucuronide	—	√	—	√
11	Adenosine2',3'-cyclic phosphate	—	—	√	√
12	4-Pyridoxolactone	√	—	—	√
13	Guanosine2',3'-cyclic phosphate	√	—	—	—
14	Pipecolic acid	√	√	√	√
15	Glycyl-L-leucine	—	—	—	√
16	Pyridoxal	—	—	—	—
17	Formyl-5-hydroxykynurenamine	—	—	—	√
18	3-(3,4-Dihydroxyphenyl)lactic acid	√	—	—	√
19	Dopaquinone	—	√	√	√
20	3-Methoxy-4-hydroxyphenylglycol aldehyde	√	—	—	—
21	Beta-Tyrosine	—	—	—	√
22	L-Tyrosine	—	√	√	√
23	3,4-Dihydroxy-trans-cinnamate	√	—	—	—
24	Homovanillin	—	—	—	—
25	D-Phenyllactic acid	—	—	—	—
26	N-Acetylarylamine	√	√	√	√
27	4-Hydroxyphenylpyruvic acid	√	√	√	√
28	Leucodopachrome	—	—	—	—

29	2-Hydroxy-3-(4-hydroxyphenyl)propenoic acid	—	—	—	—
30	Phenyllactic acid	√	—	—	√
31	Indolelactic acid	√	—	—	—
32	3-Dehydro-L-gulonate	—	—	—	—

Note: Y: Positive control group; L: Luozhen capsule low dose group; Z: Luozhen capsule medium dose group; H: Luozhen capsule high dose group. √ indicates a drug callback; - indicates that the drug has no callback.