

Figure S1 The K-means cluster diagram was used to cluster with $\log_2(\text{ratio})$ and the relative expression level of circRNA. The gray lines in each subgraph represent a line chart of the relative expression of circRNAs in a cluster under different experimental conditions. The blue lines represent the line chart of the average relative expression of all circRNAs in this cluster under different experimental conditions. Red line for reference; online for up-regulation; offline for down-regulation. The x-axis represents the experimental conditions and the y-axis represents the relative expression.

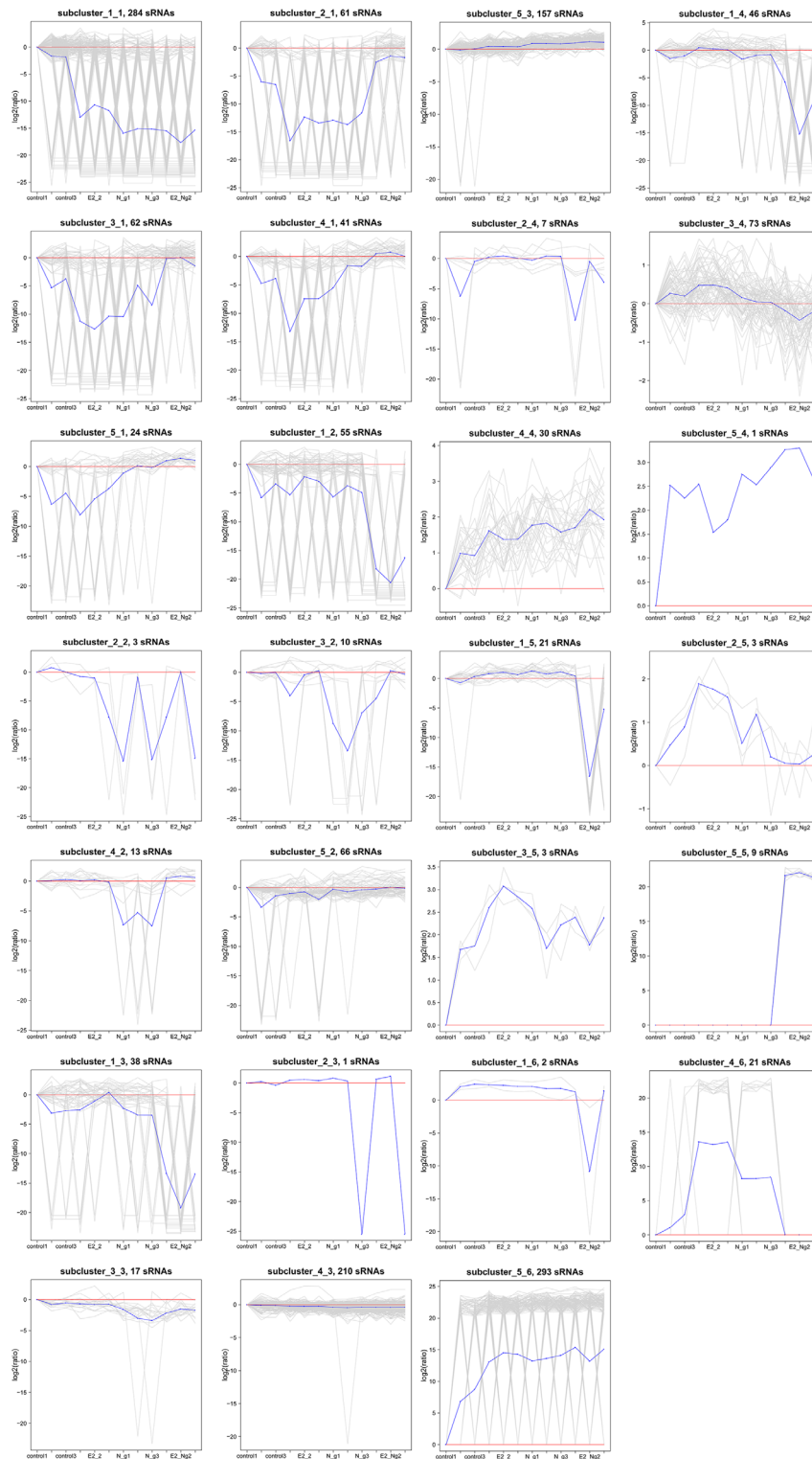


Figure S2 The SOM cluster diagram was plotted for cluster analysis according to the relative expression level of circRNAs and \log_2 (ratio). The gray lines in each subgraph represent a line chart of the relative expression of circRNAs in a cluster under different experimental conditions. The blue lines represent the line chart of the average relative expression of all circRNAs in this cluster under different experimental conditions. Red line for reference; online for up-regulation; offline for down-regulation. The x-axis represents the experimental conditions and the y-axis represents the relative expression. SOM, self-organizing feature map.

Table S1 differential expression of circRNA between gonococcal disease group and gonococcal disease + estrogen treatment group (|log₂FoldChange|> 1)

ID	log ₂ FoldChange	P value	Up/down
novel_circ_0053247	1.005	0.006	Up
novel_circ_0006039	1.024	0.011	Up
mmu_circ_0001067	1.033	0.012	Up
novel_circ_0007025	1.045	0.006	Up
novel_circ_0004284	1.087	0.008	Up
novel_circ_0015562	1.094	0.007	Up
novel_circ_0005831	1.123	0.006	Up
novel_circ_0011180	1.173	0.003	Up
novel_circ_0014946	1.183	0.004	Up
novel_circ_0009247	1.444	<0.001	Up
novel_circ_0010828	1.543	<0.001	Up
novel_circ_0004698	1.692	<0.001	Up
novel_circ_0022197	2.74	<0.001	Up
novel_circ_0022275	-4.042	<0.001	Down
novel_circ_0062043	-1.545	<0.001	Down
novel_circ_0030437	-1.467	<0.001	Down
novel_circ_0031952	-1.46	<0.001	Down
novel_circ_0014804	-1.332	0.001	Down
novel_circ_0053832	-1.163	0.002	Down
novel_circ_0007381	-1.147	0.003	Down
novel_circ_0011509	-1.114	0.007	Down
novel_circ_0031938	-1.105	0.003	Down
novel_circ_0025670	-1.085	0.006	Down
novel_circ_0004337	-1.072	0.009	Down
novel_circ_0035892	-1.063	0.007	Down
novel_circ_0049155	-1.046	0.005	Down
novel_circ_0049475	-1.028	0.005	Down

Table S2 differentially expressed metabolites between gonococcal disease group and gonococcal disease + estrogen treatment group ($|\log_2\text{FoldChange}|>1$)

ID	P value	$\log_2\text{FoldChange}$	NEG/POS	Up/down	MS name
764	0.018	-2.935	NEG	Down	
765	0.038	-1.499	NEG	Down	
724	0.033	-1.337	NEG	Down	
2071	0.006	1.005	NEG	Up	N-(3,5-Dichlorophenyl)succinimide
2087	0.036	1.03	NEG	Up	
16	0.034	1.076	NEG	Up	Xanthine
1148	0.022	1.124	NEG	Up	3,4,5-trihydroxy-6-[2-hydroxy-4-(3,5,6,7-tetrahydroxy-4-oxo-3,4-dihydro-2H-1-benzopyran-2-yl)phenoxy]oxane-2-carboxylic acid
2134	0.006	1.203	NEG	Up	
2092	0.017	1.254	NEG	Up	N-(3,5-Dichlorophenyl)succinimide
2091	0.003	1.64	NEG	Up	
1496	0.003	1.79	NEG	Up	
1466	0.001	1.95	NEG	Up	
2089	0.013	2.124	NEG	Up	
1149	0.018	2.508	NEG	Up	Irisxanthone
1147	0.035	2.549	NEG	Up	
1180	0.015	3.286	NEG	Up	
1455	0.04	7.241	NEG	Up	
2647	0.013	8.12	NEG	Up	
1768	0.048	-1.838	POS	Down	
2921	<0.001	-1.365	POS	Down	N,N'-Dimethylurea
2408	0.046	-1.229	POS	Down	
2619	0.016	-1.066	POS	Down	
817	0.001	-1.063	POS	Down	Violaceinic acid
2396	0.033	-1.058	POS	Down	
2890	0.044	1.017	POS	Up	
1373	0.001	1.037	POS	Up	
2895	0.002	1.044	POS	Up	
2636	0.031	1.072	POS	Up	
1338	0.031	1.096	POS	Up	Jacareubin
1677	0.028	1.1	POS	Up	2-Sulfotrehalose
3370	0.019	1.118	POS	Up	4-Fluorophenol
1913	0.038	1.131	POS	Up	3-[3,5-dihydroxy-4-(sulfooxy)benzoyloxy]-4,5-dihydroxybenzoic acid
1915	0.012	1.135	POS	Up	
3938	0.003	1.151	POS	Up	
1588	0.012	1.237	POS	Up	Irisxanthone
1744	<0.001	1.245	POS	Up	Deltamethrin

Table S2 (continued)

Table S2 (continued)

ID	P value	log ₂ FoldChange	NEG/POS	Up/down	MS name
3079	0.015	1.36	POS	Up	
1586	0.009	1.363	POS	Up	
1157	0.031	1.447	POS	Up	3,4,5-trihydroxy-6-(4-methoxy-1-benzofuran-5-carboxyloxy)oxane-2-carboxylic acid
1911	0.022	1.462	POS	Up	Propionyladenylate
1374	0.002	1.477	POS	Up	
1342	0.032	1.514	POS	Up	
745	0.041	1.526	POS	Up	
1341	0.012	1.531	POS	Up	
1589	0.028	1.593	POS	Up	
1627	0.044	1.625	POS	Up	
1158	0.017	1.632	POS	Up	[2,6-dihydroxy-4-({[2,3,5-trihydroxy-6-(hydroxymethyl)oxan-4-yl]oxy}carbonyl)phenyl]oxidanesulfonic acid
1740	0.021	1.722	POS	Up	
1678	0.04	1.762	POS	Up	
3950	0.024	1.856	POS	Up	
2543	0.007	1.91	POS	Up	
1735	<0.001	1.967	POS	Up	
2542	0.035	2.07	POS	Up	
2763	0.037	2.09	POS	Up	
1676	0.025	2.183	POS	Up	
1592	0.007	2.201	POS	Up	Loquatoside
1409	0.04	2.239	POS	Up	
1376	0.003	2.301	POS	Up	
1448	0.035	2.409	POS	Up	
1391	0.005	2.503	POS	Up	dTDP-4-dimethylamino-4,6-dideoxy-5-C-methyl-L-mannose
1414	0.039	2.509	POS	Up	
1378	0.008	2.549	POS	Up	
1388	0.038	2.611	POS	Up	
1375	0.023	3.07	POS	Up	3,4,5-trihydroxy-6-{{[3-(6-hydroxy-7-methoxy-2H-1,3-benzodioxol-5-yl)prop-2-enyl]oxy}oxane-2-carboxylic acid
1415	0.006	3.618	POS	Up	Auranofin
2603	0.037	4.238	POS	Up	N-Acetyl-D-glucosamine 6-phosphate
1397	0.006	4.36	POS	Up	
1380	0.001	4.47	POS	Up	2-[(3-{4-[(6-carboxy-3,4,5-trihydroxyoxan-2-yl)oxy]-3-methoxyphenyl}prop-2-enyl)oxy]-3-hydroxybutanedioic acid
2752	0.046	6.524	POS	Up	
2597	0.004	7.044	POS	Up	

NEG, negative ion mode; POS, positive ion mode; MS, mass spectrometry.

Table S3 Statistical table of differential metabolite enrichment pathways between gonococcal disease group and gonococcal disease + estrogen treatment group

NEG/POS	Comparison	Pathway	Hits Cpd	P value	FDR
NEG	Neisseria gonorrhoeae-blank	Purine metabolism	Xanthine cpd:C00385	0.048	1
NEG	Neisseria gonorrhoeae estrogen-blank	Taurine and hypotaurine metabolism	Taurine cpd:C00245	0.028	1
NEG	Neisseria gonorrhoeae estrogen-blank	Biosynthesis of unsaturated fatty acids	Oleic acid cpd:C00712	0.14	1
NEG	Neisseria gonorrhoeae estrogen-blank	Fatty acid biosynthesis	Oleic acid cpd:C00712	0.143	1
NEG	Neisseria gonorrhoeae estrogen-blank	Primary bile acid biosynthesis	Taurine cpd:C00245	0.152	1
NEG	Neisseria gonorrhoeae estrogen-blank	Purine metabolism	Xanthine cpd:C00385	0.218	1
NEG	Estrogen-Neisseria gonorrhoeae estrogen	Biosynthesis of unsaturated fatty acids	Oleic acid cpd:C00712	0.058	1
NEG	Estrogen-Neisseria gonorrhoeae estrogen	Fatty acid biosynthesis	Oleic acid cpd:C00712	0.06	1
NEG	Neisseria gonorrhoeae estrogen-gonococcus	Purine metabolism	Xanthine cpd:C00385	0.048	1
POS	Neisseria gonorrhoeae-blank	Glutathione metabolism	Glutathione cpd:C00051; L-Glutamic acid cpd:C00025	0.002	0.156
POS	Neisseria gonorrhoeae-blank	D-Glutamine and D-glutamate metabolism	L-Glutamic acid cpd:C00025	0.014	0.576
POS	Neisseria gonorrhoeae-blank	Nitrogen metabolism	L-Glutamic acid cpd:C00025	0.025	0.689
POS	Neisseria gonorrhoeae-blank	Histidine metabolism	L-Glutamic acid cpd:C00025	0.042	0.772
POS	Neisseria gonorrhoeae-blank	Butanoate metabolism	L-Glutamic acid cpd:C00025	0.061	0.772
POS	Neisseria gonorrhoeae-blank	Alanine, aspartate and glutamate metabolism	L-Glutamic acid cpd:C00025	0.066	0.772
POS	Neisseria gonorrhoeae-blank	Porphyrin and chlorophyll metabolism	L-Glutamic acid cpd:C00025	0.074	0.772
POS	Neisseria gonorrhoeae-blank	Glycerophospholipid metabolism	Choline cpd:C00114	0.082	0.772
POS	Neisseria gonorrhoeae-blank	Glycine, serine and threonine metabolism	Choline cpd:C00114	0.085	0.772
POS	Neisseria gonorrhoeae-blank	Arginine and proline metabolism	L-Glutamic acid cpd:C00025	0.119	0.973
POS	Neisseria gonorrhoeae-blank	Aminoacyl-tRNA biosynthesis	L-Glutamic acid cpd:C00025	0.181	1
POS	Neisseria gonorrhoeae estrogen-blank	Arginine and proline metabolism	L-Glutamic acid cpd:C00025; L-Proline cpd:C00148; Creatine cpd:C00300	0.001	0.074
POS	Neisseria gonorrhoeae estrogen-blank	Aminoacyl-tRNA biosynthesis	L-Tryptophan cpd:C00078; L-Proline cpd:C00148; L-Glutamic acid cpd:C00025	0.003	0.138
POS	Neisseria gonorrhoeae estrogen-blank	Glutathione metabolism	Glutathione cpd:C00051; L-Glutamic acid cpd:C00025	0.006	0.176
POS	Neisseria gonorrhoeae estrogen-blank	Glycine, serine and threonine metabolism	Choline cpd:C00114; Creatine cpd:C00300	0.009	0.186

Table S3 (continued)

Table S3 (continued)

NEG/POS	Comparison	Pathway	Hits Cpd	P value	FDR
POS	Neisseria gonorrhoeae estrogen-blank	D-Glutamine and D-glutamate metabolism	L-Glutamic acid cpd:C00025	0.024	0.402
POS	Neisseria gonorrhoeae estrogen-blank	Nitrogen metabolism	L-Glutamic acid cpd:C00025	0.044	0.597
POS	Neisseria gonorrhoeae estrogen-blank	Histidine metabolism	L-Glutamic acid cpd:C00025	0.072	0.843
POS	Neisseria gonorrhoeae estrogen-blank	Butanoate metabolism	L-Glutamic acid cpd:C00025	0.104	1
POS	Neisseria gonorrhoeae estrogen-blank	Alanine, aspartate and glutamate metabolism	L-Glutamic acid cpd:C00025	0.113	1
POS	Neisseria gonorrhoeae estrogen-blank	Porphyrin and chlorophyll metabolism	L-Glutamic acid cpd:C00025	0.126	1
POS	Neisseria gonorrhoeae estrogen-blank	Glycerophospholipid metabolism	Choline cpd:C00114	0.139	1
POS	Neisseria gonorrhoeae estrogen-blank	Tryptophan metabolism	L-Tryptophan cpd:C00078	0.182	1
POS	Estrogen-Neisseria gonorrhoeae estrogen	Aminoacyl-tRNA biosynthesis	L-Phenylalanine cpd:C00079; L-Proline cpd:C00148; L-Glutamic acid cpd:C00025	0	0.035
POS	Estrogen-Neisseria gonorrhoeae estrogen	Arginine and proline metabolism	L-Glutamic acid cpd:C00025; L-Proline cpd:C00148	0.005	0.223
POS	Estrogen-Neisseria gonorrhoeae estrogen	Phenylalanine, tyrosine and tryptophan biosynthesis	L-Phenylalanine cpd:C00079	0.011	0.288
POS	Estrogen-Neisseria gonorrhoeae estrogen	D-Glutamine and D-glutamate metabolism	L-Glutamic acid cpd:C00025	0.014	0.288
POS	Estrogen-Neisseria gonorrhoeae estrogen	Nitrogen metabolism	L-Glutamic acid cpd:C00025	0.025	0.413
POS	Estrogen-Neisseria gonorrhoeae estrogen	Phenylalanine metabolism	L-Phenylalanine cpd:C00079	0.031	0.42
POS	Estrogen-Neisseria gonorrhoeae estrogen	Histidine metabolism	L-Glutamic acid cpd:C00025	0.042	0.489
POS	Estrogen-Neisseria gonorrhoeae estrogen	Butanoate metabolism	L-Glutamic acid cpd:C00025	0.061	0.553
POS	Estrogen-Neisseria gonorrhoeae estrogen	Alanine, aspartate and glutamate metabolism	L-Glutamic acid cpd:C00025	0.066	0.553
POS	Estrogen-Neisseria gonorrhoeae estrogen	Glutathione metabolism	L-Glutamic acid cpd:C00025	0.071	0.553
POS	Estrogen-Neisseria gonorrhoeae estrogen	Porphyrin and chlorophyll metabolism	L-Glutamic acid cpd:C00025	0.074	0.553

NEG, negative ion mode; POS, positive ion mode; FDR, false discovery rate.

Table S4 Metabolite Mapping statistics of different metabolites among treatment groups

NEG/POS	Comparison	HMDB	KEGG	Query	Match
NEG	Neisseria gonorrhoeae-blank	HMDB0000292	C00385	Xanthine	Xanthine
NEG	Estrogen-blank	HMDB0000847	C01601	Pelargonate	Pelargonic acid
NEG	Neisseria gonorrhoeae estrogen-blank	HMDB0000251	C00245	Taurine	Taurine
NEG	Neisseria gonorrhoeae estrogen-blank	HMDB0000744	C00711	Malic acid	Malic acid
NEG	Neisseria gonorrhoeae estrogen-blank	HMDB0000292	C00385	Xanthine	Xanthine
NEG	Neisseria gonorrhoeae estrogen-blank	HMDB0000847	C01601	Pelargonate	Pelargonic acid
NEG	Neisseria gonorrhoeae estrogen-blank	HMDB0000207	C00712	Oleic acid	Oleic acid
NEG	Estrogen-Neisseria gonorrhoeae estrogen	HMDB0000744	C00711	Malic acid	Malic acid
NEG	Estrogen-Neisseria gonorrhoeae estrogen	HMDB0000207	C00712	Oleic acid	Oleic acid
NEG	Neisseria gonorrhoeae estrogen-gonococcus	HMDB0000292	C00385	Xanthine	Xanthine
POS	Neisseria gonorrhoeae-blank	HMDB0000097	C00114	Choline	Choline
POS	Neisseria gonorrhoeae-blank	HMDB0000148	C00025	Glutamate	L-Glutamic acid
POS	Neisseria gonorrhoeae-blank	HMDB0000125	C00051	Glutathione	Glutathione
POS	Neisseria gonorrhoeae-blank	HMDB00033244	C14214	Di-n-butyl phthalate	Dibutyl phthalate
POS	Neisseria gonorrhoeae-blank	HMDB00035228		Theaspiron A	Theaspiron A
POS	Neisseria gonorrhoeae-blank	HMDB00034495		6,10,14-Trimethyl-5,9,13- pentadecatrien-2-one	6,10,14-Trimethyl-5,9,13- pentadecatrien-2-one
POS	Estrogen-blank	HMDB00034146	C13846	Stearamide	Octadecanamide
POS	Neisseria gonorrhoeae estrogen-blank	HMDB0000097	C00114	Choline	Choline
POS	Neisseria gonorrhoeae estrogen-blank	HMDB0000162	C00148	Proline	L-Proline
POS	Neisseria gonorrhoeae estrogen-blank	HMDB0000148	C00025	Glutamate	L-Glutamic acid
POS	Neisseria gonorrhoeae estrogen-blank	HMDB0000929	C00078	Tryptophan	L-Tryptophan
POS	Neisseria gonorrhoeae estrogen-blank	HMDB0000125	C00051	Glutathione	Glutathione
POS	Neisseria gonorrhoeae estrogen-blank	HMDB0000805	C02237	(R)-(+)-2-Pyrrolidone-5- carboxylic acid	Pyrrolidonecarboxylic acid
POS	Neisseria gonorrhoeae estrogen-blank	HMDB0000064	C00300	Creatine	Creatine

Table S4 (continued)

Table S4 (continued)

NEG/POS	Comparison	HMDB	KEGG	Query	Match
POS	Estrogen-Neisseria gonorrhoeae estrogen	HMDB0031641		Pyrrolidine	Pyrrolidine
POS	Estrogen-Neisseria gonorrhoeae estrogen	HMDB0000162	C00148	Proline	L-Proline
POS	Estrogen-Neisseria gonorrhoeae estrogen	HMDB0000159	C00079	Phenylalanine	L-Phenylalanine
POS	Estrogen-Neisseria gonorrhoeae estrogen	HMDB0000148	C00025	Glutamate	L-Glutamic acid
POS	Estrogen-Neisseria gonorrhoeae estrogen	HMDB0000805	C02237	(R)-(+)-2-Pyrrolidone-5-carboxylic acid	Pyrrolidonecarboxylic acid

NEG, negative ion mode; POS, positive ion mode; KEGG, Kyoto Encyclopedia of Genes and Genomes.