Electronic Supplementary Material (ESI) for Molecular BioSystems.

Supplementary Table 1. Potential urinary biomarkers identified by UPLC/ESI-Q/TOF-HDMS

NO.	Rt	m/z determined	Ion form	Molecular Formula	Metabolite Name	MS/MS	Pathway Name	Trend	VIP	Gen
1	1	112.086	[M+H]+	$C_5H_9N_3$	Histamine	58(-C3H8N) 68(-C4H6N) 81(-C4H5N2) 83(-C4H7N2) 95(-C5H7N2)	Histidine metabolism	↓	0.9514	√
2	1.22	150.0543	[M+H]+	C8H7NO2	5,6-Dihydroxyindole	78(-C5H4N) 92(-C6H6N) 108(-C6H4O2) 118(-C8H5O) 122(-C7H5O2) 133(-C8H6NO)	Tyrosine metabolism	↓	4.9423	√
3	1.3	121.064	[M+H]+	C8H8O	Phenylacetaldehyde	43(-C2H3O) 51(-C4H3) 77(-C6H5) 91(-C7H7) 103(-C8H7)	Phenylalanine metabolism	↓	6.4374	√
4	1.3	138.0903	[M+H]+	C8H11NO	Tyramine	51(-C4H3) 77(-C6H5) 91(-C7H7) 93(-C7H9) 103(-C8H7) 121(-C8H9O)	Tyrosine metabolism	↓	7.2987	√
5	1.55	102.0901	[M+H]+	C5H11NO	Betaine aldehyde	58(-C3H4N) 72(-C4H10N) 87(-C4H9NO)	Glycine, serine and threonine metabolism	↑	0.398	√
6	1.62	613.1714	[M+H]+	C20H32N6O12S2	Oxidized glutathione	130(-C5H7NO3) 177(-C5H9N2O3S) 355(-C10H18N4O6S2) 409(-C13H21N4O7S2) 484(- C15H26O9N5S2)	Glutathione metabolism	↑	1.7246	√
7	1.96	155.0333	[M+H]+	C7H6O4	Gentisic acid	53(-C4H5) 81(-C5H5O6) 108(-C6H4O2) 109(-C6H5O2) 153(-C7H5O4)	Tyrosine metabolism	↑	0.4325	√
8	2.13	73.0282	[M+H]+	C3H4O2	Methylglyoxal	55(-C3H3O) 56(-C2O2) 73(-C3H5O2)	Glycine, serine and threonine metabolism	↑	1.3255	√
9	2.14	225.0819	[M+H]+	C10H12N2O4	5-Hydroxykynurenine	74(-C2H4NO2) 108(-C6H6NO) 136(-C7H6NO2) 151(-C8H9NO2) 179(-C9H11N2O2) 208(-C10H10NO4)	Tryptophan metabolism	↑	3.5933	√
10	3.3	173.0904	[M-H]-	C7H14N2O3	N-Acetylornithine	58(-C3H8N) 85(- C4H10N2) 113(-C5H9N2O) 114(-C5H10N2O) 131(-C5H11N2O2) 144(-C6H10NO3) 157(-C7H12NO3)	Arginine biosynthesis	↓	1.8718	√
11	3.3	113.0338	[M+H]+	C4H4N2O2	Uracil	68(-C3H2NO) 70(-C3H4NO) 87(-C2H3N2O2) 96(-C4H4N2O) 113(-C4H5N2O2)	Pyrimidine metabolism	↓	0.3938	√
12	3.37	114.0538	[M-H]-	C5H9NO2	L-Proline	68(-C4H6N) 70(-C3H2O2) 86(-C3H4NO2)	Arginine and prolinemetabolism	↑	0.2581	
13	3.42	258.0406	[M-H]-	C6H14NO8P	D-Glucosamine 6-phosphate	78(-O3P) 96(-O4H2P) 198(-C4H8O7P) 240(-C6H12NO7P) 258(-C6H13NO8P)	Alanine, aspartate and glutamate metabolism	↑	0.8478	
14	3.47	325.05	[M+H]+	C9H13N2O9P	Uridylic acid	68(-C4H3O) 83(-C3H3N2O) 98(-C4H4NO2) 113(-C4H5N2O2)	Pyrimidine metabolism	↓	8.2531	√
15	3.52	171.0638	[M+H]+	C8H10O4	3,4-Dihydroxyphenylglycol	75(-C6H3)	Tyrosine	↓	1.592	√

						109(-C6H5O2) 139(-C8H10O2) 151(-C8H7O3)	metabolism			
16	3.64	128.0332	[M-H]-	C5H7NO3	Pyroglutamic acid	54(-C3H4N) 72(-C2H2NO2) 82(-C4H4NO) 1289-C5H6NO3)	Glutathione metabolism	↑	1.3196	√
17	3.64	164.069	[M-H]-	C9H11NO2	L-Phenylalanine	72(-C2H2NO2) 91(-C7H7) 103(-C8H7) 147(-C9H7O2)	Phenylalanine metabolism	↑	0.6022	
18	3.73	90.0546	[M+H]+	C3H7NO2	L-Alanine	42(-C2H7N) 44(-CH2O2) 44(-C2H6N)	Alanine, aspartate and glutamate metabolism	↓	2.8879	√
19	3.73	184.0951	[M+H]+	C9H13NO3	(-)-Epinephrine	57(-C3H7N) 79(-C6H7) 107(-C7H7O) 151(-C8H9NO2) 166(-C9H12NO2)	Tyrosine metabolism	↓	2.941	√
20	3.79	353.1384	[M-H]-	C14H22N6O3S	S-Adenosylmethioninamine	56(-C3H6N) 100(-C4H4O3) 102(-C4H8NS) 116(-C5H8O3) 134(-C5H4N5)	Arginine and proline metabolism	↑	0.9258	
21	4.3	116.0697	[M-H]-	C5H11NO2	L-Valine	56(-C3H6N) 59(-C2H3O2) 116(-C5H10O2)	Valine, leucine and isoleucine degradation	↑	0.2411	√
22	4.31	112.0377	[M-H]-	C5H7NO2	1-Pyrroline-2-carboxylic acid	66(-C4H4N) 94(-C5H4NO) 112(-C5H6NO2)	Arginine and proline metabolism	↑	0.5293	
23	4.4	189.0937	[M-H]-	C6H14N4O3	N(omega)-Hydroxyarginine	70(-C4H8N) 749-CH4N3O) 114(-C5H8NO2) 129(-C5H9N2O2) 145(-C5H13N4O) 172(-C6H10N3O3)	Arginine and proline metabolism	↑	0.1867	√
24	4.44	180.0635	[M-H]-	C9H11NO3	L-Tyrosine	74(-C2H4NO2) 93(-C7H9) 107(-C7H7O) 119(-C8H7O) 134(-C8H8NO) 136(-C8H10NO) 163(-C9H9NO2)	Tyrosine metabolism	↑	1.1665	√
25	4.54	198.0742	[M+H]+	C9H11NO4	L-Dopa	77(-C6H5) 79(-C5H3O) 919-C7H7) 93(-C6H5O) 134(-C8H8NO3) 135(-C7H3O3) 139(-C7H7O3) 152(-C8H10NO2) 181(-C9H9O4)	Tyrosine metabolism	↓	1.3572	√
26	4.59	176.0691	[M+H]+	C10H9NO2	5-Hydroxyindoleacetaldehyde	132(-C8H6NO) 146(-C9H8NO) 149(-C9H9O2) 158(-C10H8NO) 176(-C10H10NO2)	Tryptophan metabolism	↓	0.7387	√
27	4.69	134.0586	[M-H]-	C8H9NO	Phenylacetamide	89(-C7H7) 99(-C6H5O) 116(-C8H6O) 117(-C8H7O) 134(-C8H7NO)	Phenylalanine metabolism	↑	0.4177	√
28	4.85	332.0711	[M+H]+	C10H14N5O6P	Deoxyadenosine monophosphate	53(-C4H5) 81(-C3H3N3) 119(-C5H3N4) 136(-C5H6N5) 270(-C9H7N2O6P)	Purine metabolism	↑	1.6327	
29	4.97	166.0487	[M+H]+	C8H7NO3	Formylanthranilic acid	65(-C4HO) 77(-C6H5) 92(-C6H6N) 120(-C7H6NO) 148(-C8H6NO2)	Tryptophan metabolism	↓	0.5205	

30	5.22	133.0633	[M+H]+	C4H8N2O3	Ureidopropionic acid	73(-C2H5N2O) 87(-C3HN2O7) 90(-C3H8NO2) 115(-C4H7N2O2)	Pyrimidine metabolism	↑	6.4223	√
31	5.22	341.1191	[M-H]-	C12H22O11	Maltose	59(-C2H4O2) 73(-C3H5O2) 101(-C4H5O3) 119(-C4H7O4) 161(-C6H9O5) 179(-C6H11O6) 221(-C8H13O7) 281(-C10H17O9)	Starch and sucrose metabolism	↑	2.036	
32	5.5	132.0281	[M-H]-	C4H7NO4	L-Aspartic Acid	59(-C2H3O2) 72(-C3H4O2) 88(-C3H6NO2) 115(-C4H5NO3)	Alanine, aspartate and glutamate metabolism	↓	0.9844	
33	5.55	76.0391	[M+H]+	C2H5NO2	Glycine	30(-CH4N) 47(-CH3O2)	Glutathione metabolism	↑	4.8888	
34	5.58	346.0661	[M-H]-	C10H14N5O7P	Adenosine monophosphate	78(-O3P) 96(-H2O4P) 134(-C5H4N5) 211(-C5H8O7P)	Purine metabolism	↑	0.2999	
35	5.62	321.0532	[M-H]-	C10H15N2O8P	5-Thymidylic acid	78(-O3P) 96(-H2O4P) 125(-C5H5N2O2) 176(-C5H6O5P) 195(-C5H7O6P)	-	↑	0.477	√
36	5.85	136.0382	[M-H]-	C7H7NO2	Anthranilic acid	75(-C6H4) 90(-C6H5N) 92(-C6H7N)	Tryptophan metabolism	↓	0.5265	√
37	6.42	192.0641	[M-H]-	C10H11NO3	Phenylacetylglycine	74(-C2H4NO20 91(-C7H7) 1929-C10H10NO3)	Phenylalanine metabolism	↑	0.4446	√
38	6.63	275.1282	[M-H]-	C11H20N2O6	Saccharopine	84(-C4H6NO) 87(-C4H6O2) 102(-C4H8NO2) 128(-C6H10NO2) 129(-C6H11NO2) 130(-C5H6O4) 145(-C6H13N2O2) 70(- C9H16NO2) 187(-C8H15N2O3) 196(-C9H8NO4) 213(-C9H13N2O4) 231(-C10H19N2O4) 240(-C11H14NO5) 257(-C11H17N2O5)	Lysine degradation	↑	0.223	√
39	6.75	72.9914	[M-H]-	C2H2O3	Glyoxylic acid	41(-C2HO) 43(-C2H3O) 71(-C2HO3)	Glycine, serine and threonine metabolism	↓	0.2077	
40	6.78	305.0112	[M-H]-	C9H11N2O8P	Deoxyuridylic acid	78(-O3P) 96(-H2O4P) 111(-C4H3N2O2) 150(-C3H3O5P) 176(-C5H5O5P) 195(-C5H8O6P) 264(-C8H11NO7P)	Pyrimidine metabolism	↑	1.1052	
41	6.81	155.0112	[M-H]-	C5H4N2O4	Orotic acid	67(-C3HNO) 68(-C3H2NO) 111(-C4H3N2O2)	Pyrimidine metabolism	↓	0.2625	
42	6.91	169.0324	[M+H]+	C5H4N4O3	Uric acid	41(-CHON) 69(-C2N2O) 96(-C3H3N2O2) 97(-C3H3N3O) 123(-C4H3N4O) 124(-C4H2N3O2)	Purine metabolism	↑	1.8556	√
43	6.91	181.051	[M-H]-	C9H10O4	3-Methoxy-4-hydroxyphenylglycolaldehyde	121(-C7H5O2) 151(-C8H7O3) 163(-C9H7O3)	Tyrosine metabolism	↑	1.1408	
44	7.05	137.0223	[M-H]-	C7H6O3	2,5-Dihydroxybenzaldehyde	81(-C5H5O) 108(-C6H4O2) 109(-C6H5O2) 136(-C7H5O3)	Tyrosine metabolism	↓	1.2034	√

45	7.96	386.0138	[M-H]-	C9H15N3O10P2	Deoxycytidine diphosphate	59(-C2H3O2) 85(-C4H5O2) 110(-C4H4N3O) 176(-H3O7P2) 158(-C6H8N2O3) 256(-C5H7O8P2) 274(-C5H9O9P2) 3069-C9H13N3O7P)	Pyrimidine metabolism	↑	0.2833	√
46	8.36	227.1083	[M+H]+	C9H14N4O3	Carnosine	83(-C4H7N2) 95(-C5H5N2) 110(-C5H9N3) 122(-C6H8N3) 156(-C6H10N3O2) 164(-C8H12N4) 181(-C8H13N4O) 210(-C9H12N3O3)	Histidine metabolism	↓	2.31	
47	8.54	193.0315	[M-H]-	C6H10O7	D-Glucuronic acid	59(-C2H3O2) 73(-C3H5O2) 89(-C3H5O3) 102(-C4H6O3) 113(-C5H5O3) 133(-C5H9O4) 163(-C6H11O5)	-	↓	1.499	√
48	8.69	442.0178	[M-H]-	C10H15N5O11P2	Guanosine diphosphate	150(-C5H4N5O) 176(-C10H15N5O11P2) 264(-C10H10N5O4) 362(-C10H13N5O8P)	Purine metabolism	↑	0.9886	√

“√”denote biomarkers that geniposide could regulate.

Supplementary table 2. Potential targets and possible signaling patheways

NO.	Targets	Pathway
1	Glucagon	Neuroactive ligand-receptor interaction;Glucagon signaling pathway
2	Apoptosis regulator Bcl-2	Amyotrophic lateral sclerosis (ALS);Apoptosis; Colorectal cancer; Epstein-Barr virus infection; HIF-1 signaling pathway;Hepatitis B; MicroRNAs in cancer PI3K-Akt signaling pathway; Pathways in cancer Prostate cancer; Protein processing in endoplasmic reticulum; Small cell lung cancer; Sphingolipid signaling pathway; Toxoplasmosis; Tuberculosis
3	Hemeoxygenase 1	NRF2 pathway;Nuclear Receptors Meta-Pathway;Oxidative Stress; Transcriptional activation by NRF2;miR-targeted genes in epithelium - TarBase
4	Neuromodulin	-
5	Glutathione S-transferase Mu 1	-
6	Glutathione S-transferase Mu 2	-
7	PhospholipaseB1,membrane-associated	-