

Supplementary Table 1 Identification results of chemical components in TWA

No.	Retention time (min)	Adducts	Name of Prototype	Experimental m/z	Theoretical m/z	Mass Error (ppm)	Formula
1	0.77	[M+H] ⁺	Arginine	175.1188	175.1190	-1.15	C ₆ H ₁₄ N ₄ O ₂
2	0.79	[M+H] ⁺	Histidine	156.0766	156.0768	-0.72	C ₆ H ₉ N ₃ O ₂
3	0.86	[M+FA-H] ⁻	Maltotriose	549.1676	549.1672	0.77	C ₁₈ H ₃₂ O ₁₆
4	0.88	[M+H] ⁺	L-proline	116.0709	116.0706	2.79	C ₅ H ₉ NO ₂
5	0.88	[M+H] ⁺	Guvacine	128.0707	128.0706	0.53	C ₆ H ₉ NO ₂
6	0.90	[M-H] ⁻	Sucrose	341.1088	341.1089	-0.43	C ₁₂ H ₂₂ O ₁₁
7	1.24	[M+H] ⁺	Adenine	136.0617	136.0618	-0.62	C ₅ H ₅ N ₅
8	1.29	[M+H] ⁺	Guvacoline	142.0862	142.0863	-0.45	C ₇ H ₁₁ NO ₂
9	1.31	[M+H] ⁺	Arecoline	156.1018	156.1019	-0.87	C ₈ H ₁₃ NO ₂
10	1.35	[M-H] ⁻	Uridine	243.0618	243.0622	-1.76	C ₉ H ₁₂ N ₂ O ₆
11	1.43	[M+H] ⁺	Adenosine	268.1036	268.1041	-1.57	C ₁₀ H ₁₃ N ₅ O ₄
12	1.51	[M+H] ⁺	Guanosine	284.0987	284.0990	-0.76	C ₁₀ H ₁₃ N ₅ O ₅
13	1.51	[M+H] ⁺	Guanine	152.0566	152.0567	-0.88	C ₅ H ₅ N ₅ O

No.	Retention time (min)	Adducts	Name of Prototype	Experimental m/z	Theoretical m/z	Mass Error (ppm)	Formula
14	1.51	[M+H] ⁺	Cordycepin	252.1087	252.1091	-1.50	C ₁₀ H ₁₃ N ₅ O ₃
15	1.58	[M+H] ⁺	L-leucine	132.1019	132.1019	-0.05	C ₆ H ₁₃ NO ₂
16	1.75	[M+H] ⁺	Gallic acid	171.0286	171.0288	-0.92	C ₇ H ₆ O ₅
17	1.94	[M+H] ⁺	Hordenine	166.1226	166.1227	-0.40	C ₁₀ H ₁₅ NO
18	2.05	[M+H] ⁺	L-phenylalanine	166.0862	166.0863	-0.42	C ₉ H ₁₁ NO ₂
19	3.45	[M+H-H ₂ O] ⁺	5-hydroxymethylfurfural	109.0289	109.0284	4.13	C ₆ H ₆ O ₃
20	5.55	[2M+H] ⁺	L-tryptophan	409.1861	205.0972	-2.28	C ₁₁ H ₁₂ N ₂ O ₂
21	5.70	[M-H] ⁻	Neochlorogenic acid	353.0883	353.0878	1.33	C ₁₆ H ₁₈ O ₉
22	6.67	[M+H] ⁺	Procyanidin b1	579.1486	579.1497	-1.89	C ₃₀ H ₂₆ O ₁₂
23	7.21	[M-H] ⁻	Catechin	289.0719	289.0717	0.32	C ₁₅ H ₁₄ O ₆
24	7.43	[M-H] ⁻	Cryptochlorogenic acid	353.0881	353.0878	0.84	C ₁₆ H ₁₈ O ₉
25	7.54	[M+H] ⁺	Isovanillic acid	169.0493	169.0496	-1.28	C ₈ H ₈ O ₄
26	7.74	[M+Na] ⁺	Syringin	395.1304	395.1312	-2.16	C ₁₇ H ₂₄ O ₉
27	7.75	[M-H] ⁻	Chlorogenic acid	353.0879	353.0878	0.40	C ₁₆ H ₁₈ O ₉

No.	Retention time (min)	Adducts	Name of Prototype	Experimental m/z	Theoretical m/z	Mass Error (ppm)	Formula
28	7.87	[M-H]-	5-o-feruloylquinic acid	367.1033	367.1034	-0.47	C ₁₇ H ₂₀ O ₉
29	7.88	[M+H]+	Caffeic acid	181.0491	181.0496	-2.66	C ₉ H ₈ O ₄
30	7.93	[M+FA-H]-	Amygdalin	502.1567	502.1566	0.15	C ₂₀ H ₂₇ NO ₁₁
31	8.28	[M+H]+	Scopolin	355.1017	355.1024	-1.93	C ₁₆ H ₁₈ O ₉
32	8.76	[M-H]-	L-epicatechin	289.0719	289.0717	0.43	C ₁₅ H ₁₄ O ₆
33	9.15	[M+H]+	Vicenin 2	595.1643	595.1658	-2.43	C ₂₇ H ₃₀ O ₁₅
34	9.54	[M+H]+	Isovanilline	153.0543	153.0546	-1.92	C ₈ H ₈ O ₃
35	9.78	[M+H-H ₂ O]+	P-coumaric acid	147.0437	147.0440	-2.10	C ₉ H ₈ O ₃
36	9.91	[M+FA-H]-	Paeoniflorin	525.1619	525.1614	1.18	C ₂₃ H ₂₈ O ₁₁
37	9.99	[M+H-H ₂ O]+	Coniferyl alcohol	163.0749	163.0753	-2.36	C ₁₀ H ₁₂ O ₃
38	10.28	[M+H-H ₂ O]+	Sinapyl alcohol	193.0856	193.0859	-1.53	C ₁₁ H ₁₄ O ₄
39	10.35	[M+H]+	7-hydroxycoumarin	163.0386	163.0390	-2.59	C ₉ H ₆ O ₃
40	10.44	[M+H]+	3,5-dimethoxy-4-hydroxybenzaldehyde	183.0649	183.0652	-1.46	C ₉ H ₁₀ O ₄
41	10.95	[M-H]-	Eriocitrin	595.1673	595.1668	0.80	C ₂₇ H ₃₂ O ₁₅

No.	Retention time (min)	Adducts	Name of Prototype	Experimental m/z	Theoretical m/z	Mass Error (ppm)	Formula
42	11.02	[M-H]-	Epicatechin gallate	441.0829	441.0827	0.31	C ₂₂ H ₁₈ O ₁₀
43	11.43	[M-H]-	Rhein-8-o-β-d-glucopyranoside	445.0778	445.0776	0.30	C ₂₁ H ₁₈ O ₁₁
44	11.48	[M+H]+	Ferulic acid	195.0648	195.0652	-2.00	C ₁₀ H ₁₀ O ₄
45	11.55	[M+H]+	Cynaroside	449.1073	449.1079	-1.22	C ₂₁ H ₂₀ O ₁₁
46	11.69	[M+H]+	Nicotiflorin	595.1648	595.1658	-1.58	C ₂₇ H ₃₀ O ₁₅
47	12.00	[M+H]+	Perlolyrine	265.0964	265.0972	-2.99	C ₁₆ H ₁₂ N ₂ O ₂
48	12.13	[M+H]+	Narirutin	581.1849	581.1865	-2.79	C ₂₇ H ₃₂ O ₁₄
49	12.35	[M+H]+	Rhoifolin	579.1698	579.1709	-1.76	C ₂₇ H ₃₀ O ₁₄
50	12.57	[M-H]-	Naringin	579.1717	579.1719	-0.36	C ₂₇ H ₃₂ O ₁₄
51	12.75	[M+H-H ₂ O]+	Zingerone	177.0906	177.0910	-2.15	C ₁₁ H ₁₄ O ₃
52	12.97	[M+H]+	Hesperidin	611.1954	611.1971	-2.70	C ₂₈ H ₃₄ O ₁₅
53	13.12	[M+H]+	Diosmin	609.1802	609.1814	-2.00	C ₂₈ H ₃₂ O ₁₅
54	13.39	[M+H]+	Neohesperidin	611.1954	611.1971	-2.73	C ₂₈ H ₃₄ O ₁₅
55	13.58	[M+NH ₄]+	Lobetyolin	414.2112	414.2122	-2.73	C ₂₀ H ₂₈ O ₈

No.	Retention time (min)	Adducts	Name of Prototype	Experimental m/z	Theoretical m/z	Mass Error (ppm)	Formula
56	14.21	[M+H] ⁺	Baicalin	447.0911	447.0922	-2.35	C ₂₁ H ₁₈ O ₁₁
57	14.88	[M-H] ⁻	Eriodictyol	287.0562	287.0561	0.25	C ₁₅ H ₁₂ O ₆
58	15.13	[M+H] ⁺	Glycitein	285.0748	285.0758	-3.37	C ₁₆ H ₁₂ O ₅
59	15.41	[M-H] ⁻	Luteolin	285.0407	285.0404	0.94	C ₁₅ H ₁₀ O ₆
60	15.61	[M+H] ⁺	Didymin	595.2008	595.2022	-2.16	C ₂₈ H ₃₄ O ₁₄
61	15.94	[M+H] ⁺	Torachryson-8-o-β-d-glucoside	409.1483	409.1493	-2.47	C ₂₀ H ₂₄ O ₉
62	15.99	[M+H] ⁺	Poncirin	595.2008	595.2022	-2.24	C ₂₈ H ₃₄ O ₁₄
63	16.03	[M-H] ⁻	Emodin-8-beta-d-glucoside	431.0982	431.0984	-0.51	C ₂₁ H ₂₀ O ₁₀
64	16.76	[M-H] ⁻	Naringenin	271.0612	271.0612	-0.01	C ₁₅ H ₁₂ O ₅
65	16.90	[M+H-H ₂ O] ⁺	Hexahydrocurcumin	357.1688	357.1696	-2.25	C ₂₁ H ₂₆ O ₆
66	16.98	[M-H] ⁻	Apigenin	269.0458	269.0455	0.83	C ₁₅ H ₁₀ O ₅
67	17.02	[M+H] ⁺	Tectorigenin	301.0699	301.0707	-2.57	C ₁₆ H ₁₂ O ₆
68	17.70	[M-H] ⁻	Baicalein	269.0457	269.0455	0.46	C ₁₅ H ₁₀ O ₅
69	18.13	[M+H] ⁺	Perillyl alcohol	153.1270	153.1274	-2.76	C ₁₀ H ₁₆ O

No.	Retention time (min)	Adducts	Name of Prototype	Experimental m/z	Theoretical m/z	Mass Error (ppm)	Formula
70	18.17	[M+H] ⁺	Isosinensetin	373.1271	373.1282	-2.94	C ₂₀ H ₂₀ O ₇
71	18.26	[M+H] ⁺	Isopimpinellin	247.0594	247.0601	-2.64	C ₁₃ H ₁₀ O ₅
72	18.71	[M-H] ⁻	Aloeemodin	269.0456	269.0455	0.34	C ₁₅ H ₁₀ O ₅
73	18.83	[M+H] ⁺	6-demethoxytangeretin	343.1167	343.1176	-2.71	C ₁₉ H ₁₈ O ₆
74	18.97	[M-H] ⁻	Rhein	283.0249	283.0248	0.21	C ₁₅ H ₈ O ₆
75	19.25	[M+H] ⁺	4',5,7-trimethoxyflavone	313.1061	313.1071	-3.17	C ₁₈ H ₁₆ O ₅
76	19.51	[M+H] ⁺	Nobiletin	403.1377	403.1388	-2.66	C ₂₁ H ₂₂ O ₈
77	19.52	[M-H] ⁻	6-gingerol	293.1762	293.1758	1.16	C ₁₇ H ₂₆ O ₄
78	19.56	[M+H] ⁺	Nomilin	515.2266	515.2276	-1.85	C ₂₈ H ₃₄ O ₉
79	19.56	[M+H] ⁺	Scutellarein tetramethyl ether	343.1167	343.1176	-2.67	C ₁₉ H ₁₈ O ₆
80	19.98	[M+H-H ₂ O] ⁺	Atractylenolide iii	231.1374	231.1379	-2.43	C ₁₅ H ₂₀ O ₃
81	20.22	[M+H] ⁺	Tangeretin	373.1272	373.1282	-2.69	C ₂₀ H ₂₀ O ₇
82	20.24	[M+H] ⁺	Obacunone	455.2052	455.2065	-2.69	C ₂₆ H ₃₀ O ₇
83	20.71	[M-H] ⁻	Emodin	269.0455	269.0455	-0.01	C ₁₅ H ₁₀ O ₅

No.	Retention time (min)	Adducts	Name of Prototype	Experimental m/z	Theoretical m/z	Mass Error (ppm)	Formula
84	20.80	[M+H] ⁺	5-demethylnobiletin	389.1221	389.1231	-2.59	C ₂₀ H ₂₀ O ₈
85	21.26	[M+H-H ₂ O] ⁺	8-gingerol	305.2104	305.2111	-2.17	C ₁₉ H ₃₀ O ₄
86	21.54	[M+FA-H] ⁻	Methyl palmitate	315.2540	315.2541	-0.35	C ₁₇ H ₃₄ O ₂
87	21.57	[M+H] ⁺	Atractylenolide ii	233.1531	233.1536	-2.23	C ₁₅ H ₂₀ O ₂
88	22.30	[M-H] ⁻	Chrysophanol	253.0503	253.0506	-1.27	C ₁₅ H ₁₀ O ₄
89	22.57	[M+H] ⁺	Atractylenolide i	231.1375	231.1380	-2.14	C ₁₅ H ₁₈ O ₂
90	22.81	[M+H-H ₂ O] ⁺	10-gingerol	333.2417	333.2424	-2.18	C ₂₁ H ₃₄ O ₄
91	22.99	[M+H] ⁺	Physcion	285.0751	285.0758	-2.19	C ₁₆ H ₁₂ O ₅
92	23.21	[M+H] ⁺	8-shogaol	305.2105	305.2111	-2.20	C ₁₉ H ₂₈ O ₃
93	23.74	[M+H] ⁺	Auraptene	299.1635	299.1642	-2.21	C ₁₉ H ₂₂ O ₃

Supplementary Table 2 Identification results of the components derived from TWA decoction adsorbed into the serum

No.	Class	Parent compound	Transformation	Retention time (min)	Adducts	Experimental m/z	Theoretical m/z	Mass Error (ppm)
1	Prototype	Guvacine		1.37	[M+NH ₄] +	145.0971	145.0977	-4.096 1
2	Prototype	5-o-feruloylquinic acid		7.60	[M-H]-	367.1036	367.1035	0.3498
3	Prototype	Vicenin 2		8.99	[M-H]-	593.1519	593.1512	1.1849
4	Prototype	Rhein-8-o-β-d-glucopyranoside		10.94	[M-H]-	445.0780	445.0776	0.8738
5	Prototype	Naringenin		16.97	[M-H]-	271.0615	271.0612	1.2481
6	Prototype	Apigenin		17.26	[M-H]-	269.0453	269.0455	-0.764 2
7	Prototype	Isosinensetin		18.81	[M+H] ⁺	373.1271	373.1282	-3.025 0
8	Prototype	Nobiletin		19.49	[M+H] ⁺	403.1379	403.1387	-2.172 0

No.	Class	Parent compound	Transformation	Retention time (min)	Adducts	Experimental m/z	Theoretical m/z	Mass Error (ppm)
9	Prototype	Atractylenolide ii		21.74	[M+NH4] +	250.1798	250.1807	-3.7538
10	Metabolite	Cryptochlorogenic acid	+H2	6.08	[M+FA-H] -	401.1091	401.1089	0.3174
11	Metabolite	Chlorogenic acid	+H2	6.75	[M-H]-	355.1037	355.1035	0.5413
12	Metabolite	5-o-feruloylquinic acid	+H2	6.99	[M+FA-H] -	415.1249	415.1246	0.6468
13	Metabolite	Baicalin	+C6H8O6	9.21	[M-H]-	621.1106	621.1097	1.4060
14	Metabolite	Syringin	-H2	9.30	[M-H]-	369.1192	369.1191	0.1726
15	Metabolite	Lobetyolin	+O2	11.19	[M+H]+	429.1769	429.1755	3.2719

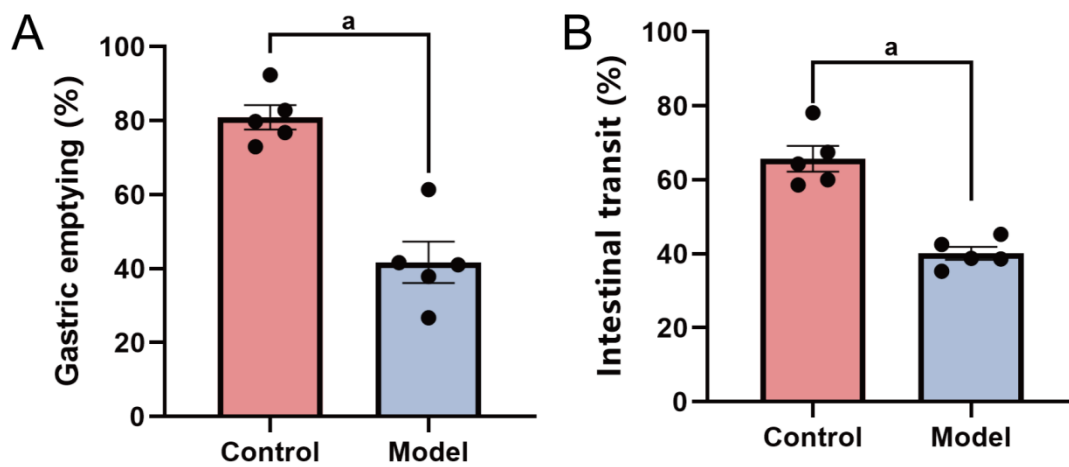
No.	Class	Parent compound	Transformation	Retention time (min)	Adducts	Experimental m/z	Theoretical m/z	Mass Error (ppm)
16	Metabolite	Baicalin	+O-H2	11.20	[M-H]-	459.0573	459.0569	0.7572
17	Metabolite	Luteolin	+C6H8O6	12.51	[M-H]-	461.0732	461.0726	1.4247
18	Metabolite	Luteolin	+SO3	13.02	[M-H]-	364.9972	364.9973	-0.0978
19	Metabolite	Rhein	+C6H8O6	13.19	[M-H]-	459.0576	459.0569	1.4423
20	Metabolite	Apigenin	+SO3	13.33	[M-H]-	349.0027	349.0024	0.8940
21	Metabolite	Glycitein	+H2O	13.54	[M+H]+	303.0858	303.0863	-1.7919
22	Metabolite	Emodin-8-beta-d-glucoside	+O	13.80	[M+H]+	449.1075	449.1078	-0.8243

No.	Class	Parent compound	Transformation	Retention time (min)	Adducts	Experimental m/z	Theoretical m/z	Mass Error (ppm)
23	Metabolite	Rhein	+SO ₃	14.68	[M-H]-	362.9822	362.9816	1.4951
24	Metabolite	Rhein-8-o-β-d-glucopyranoside	-CO	14.78	[M-H]-	417.0833	417.0827	1.2873
25	Metabolite	5-demethylnobiletin	+C ₆ H ₈ O ₆	14.91	[M+H] ⁺	565.1547	565.1552	-0.8435
26	Metabolite	Aloeemodin	+C ₆ H ₈ O ₆	15.71	[M-H]-	445.0781	445.0776	1.1126
27	Metabolite	Baicalin	-CO	16.60	[M-H]-	417.0834	417.0827	1.6344
28	Metabolite	6-gingerol	+C ₆ H ₈ O ₆	16.95	[M-H]-	469.2084	469.2079	1.0379
29	Metabolite	Emodin	+C ₆ H ₈ O ₆	17.26	[M-H]-	445.0782	445.0776	1.3721

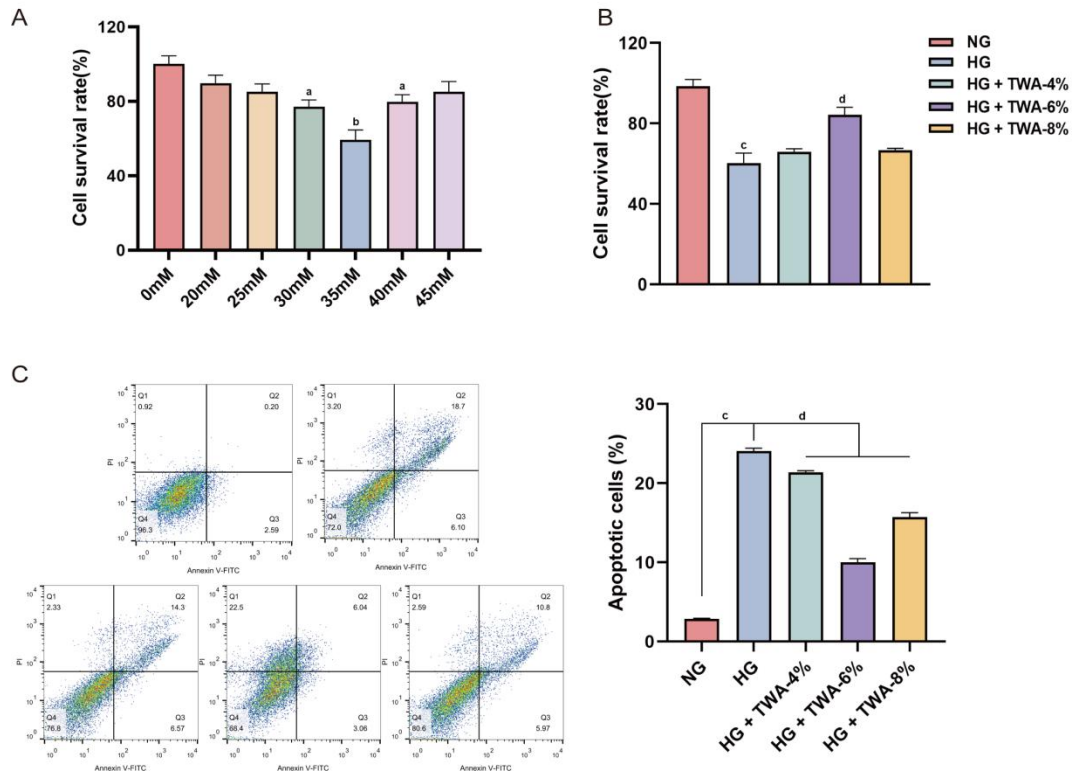
No.	Class	Parent compound	Transformation	Retention time (min)	Adducts	Experimental m/z	Theoretical m/z	Mass Error (ppm)
30	Metabolite	4',5,7-trimethoxyflavone	+O	17.29	[M+H] ⁺	329.1012	329.1020	-2.3819
31	Metabolite	Emodin	+CO	17.95	[M-H] ⁻	297.0407	297.0405	0.9325
32	Metabolite	Emodin	+SO ₃	18.41	[M-H] ⁻	349.0028	349.0024	1.3544

Supplementary Table 3 Binding ability of different compounds with Cox6a2 proteins

	Cox6a2
Nobiletin	-6
Atractylenolide II	-5.9
Guvacine	-4.2
5-o-feruloylquinic acid	-6.9
Vicenin 2	-6.4
Rhein-8-o- β -d-glucopyranoside	-6.8
Naringenin	-6
Apigenin	-6
Isosinensetin	-5.9



Supplementary Figure 1 Gastric emptying rate and Intestinal transit rate of each group (n = 5).



Supplementary Figure 2 HG modeling and TWAD-containing serum dose selection. (A) CCK-8 assay for glucose-dose screening (n = 6). (B) CCK-8 assay for titration of TWAD-containing serum (n = 6). (C) Flow cytometric analysis of apoptosis (n = 3). Data are mean±SEM. ^a*P* < 0.05 vs. 0mM; ^b*P* < 0.01 vs. 0mM; ^c*P* < 0.01 vs. NG; ^d*P* < 0.01 vs. HG.