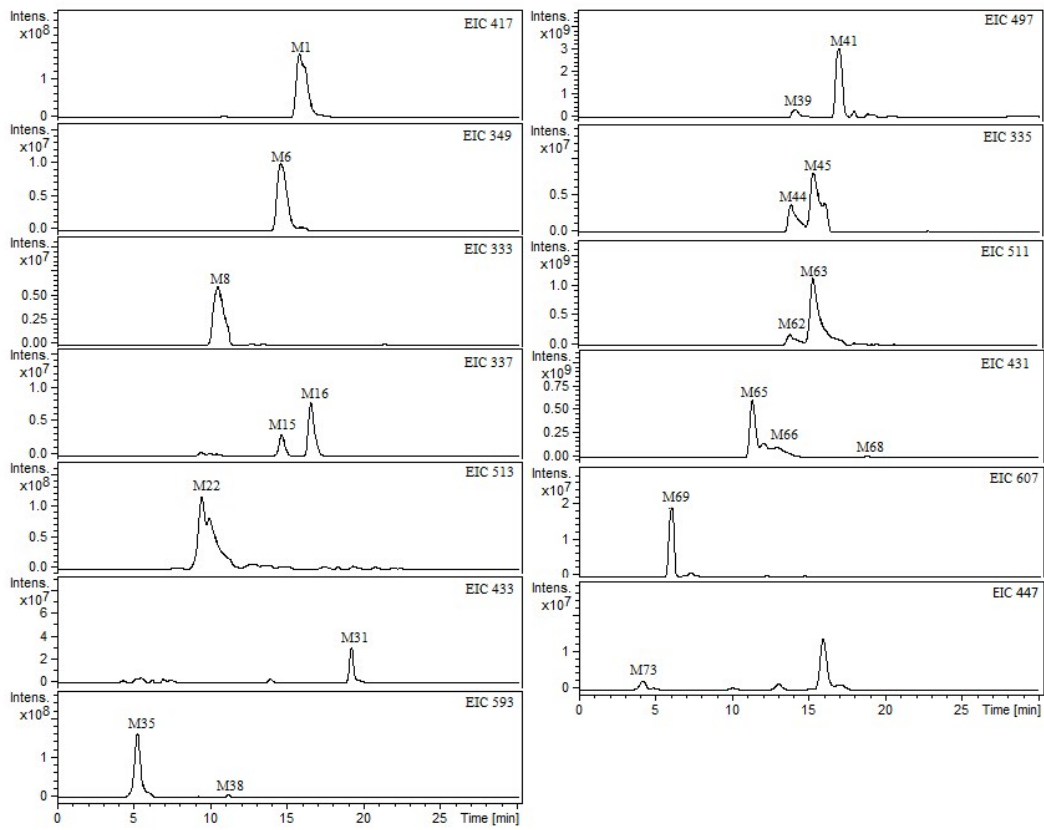
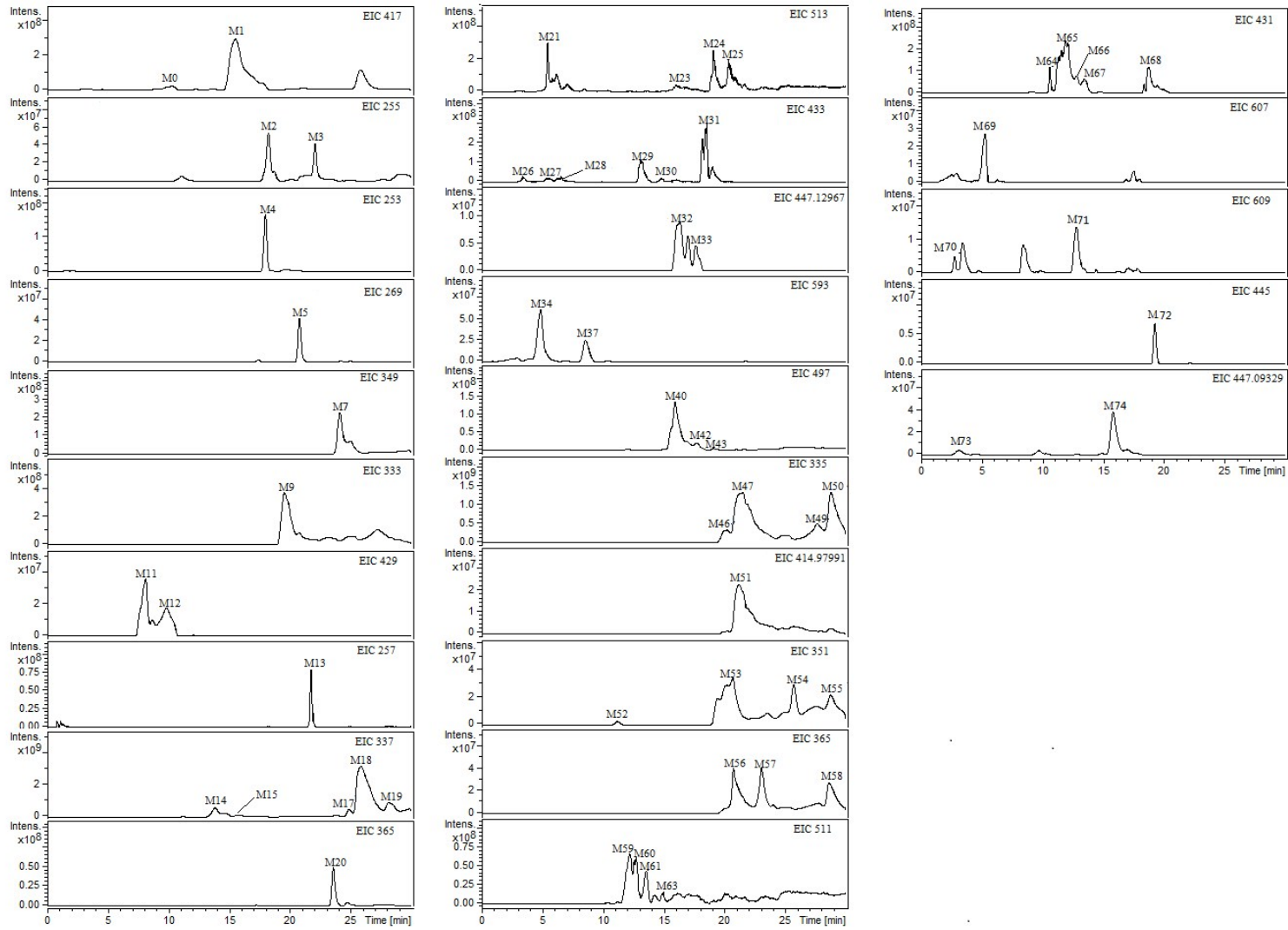


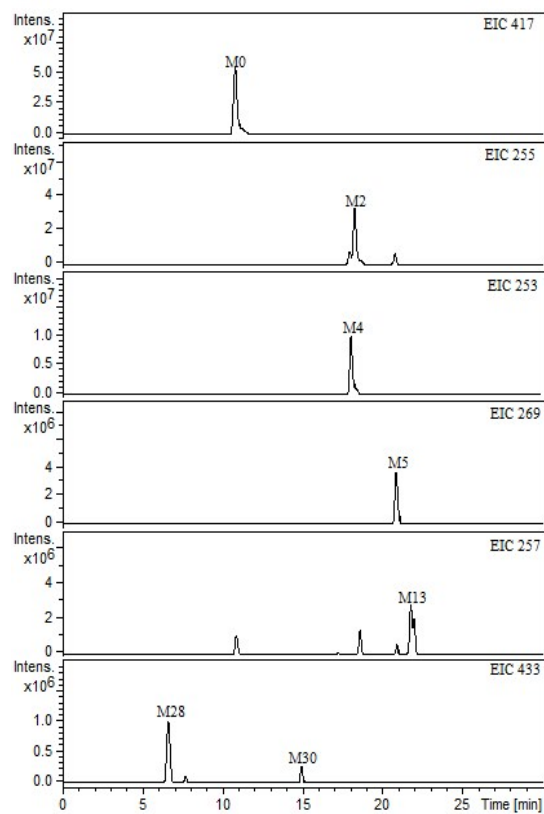
Supplementary Fig.1. Base peak intensity chromatograms (BPCs) of biological samples in negative ion mode. P0, B0, U0 and F0 represent blank samples of plasma, bile, urine and feces from rats; P1, B1, U1 and F1 represent plasma, bile, urine and feces samples from rats after oral administration of liquiritin.

A

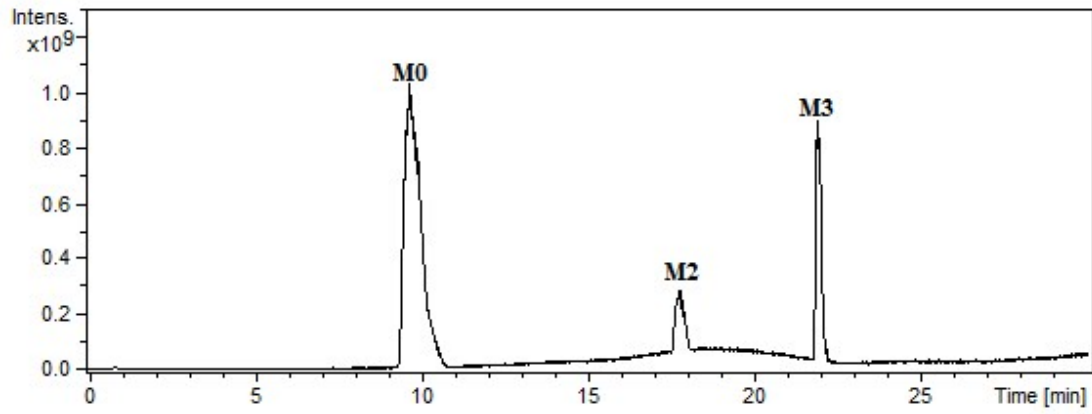


B

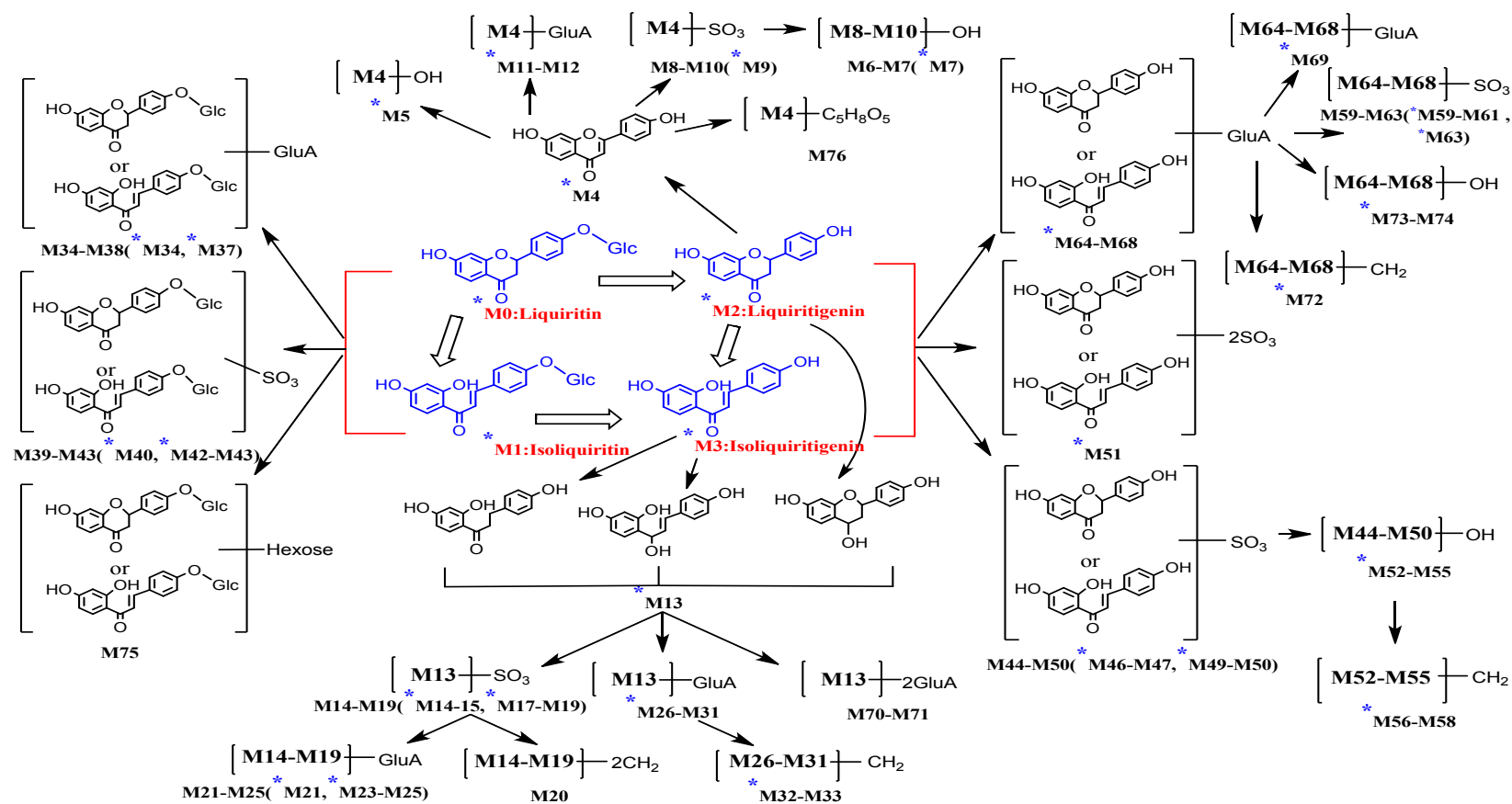
C



Supplementary Fig 2. Extracted ion chromatograms (EICs) for metabolites of liquiritin in rats: (A) bile; (B) urine; (C) feces. M0 represents parent drug; M1–M76 represent metabolites of liquiritin.



Supplementary Fig 3 BPC chromatograms of standard substances of liquiritin, liquiritigenin and isoliquiritigenin.



Supplementary Fig.4 Proposed metabolic pathways of liquiritin in rats. M1, M2 and M3 were the major metabolites of liquiritin.

The kidney is the major elimination pathway after oral administration of liquiritin, and the metabolites detected in rat urine were marked with *.

Supplementary Table Potential new metabolites of liquiritin detected and tentatively identified by UHPLC-FT-ICR MS method in rats

No.	t _R (min)	[M-H] ⁻			MS/MS	Formula	Metabolite description	Matrix
		Calculated Mass (Da)	Observed Mass (Da)	Error (ppm)				
M4	17.94	253.05063	253.05029	1.34	224.04719, 135.00929	C ₁₅ H ₁₀ O ₄	Deglycosylation+dehydrogenation	U, F
M5	20.77	269.04555	269.04530	0.91	224.04718, 253.05063	C ₁₅ H ₁₀ O ₅	Deglycosylation+dehydrogenation+hydroxylation	U, F
M6	14.70	349.00236	349.00198	1.10	269.04502	C ₁₅ H ₁₀ O ₈ S	Deglycosylation+ isomerization+sulfation+ hydroxylation+ dehydrogenation	B
M7	24.07	349.00236	349.00210	0.75	269.04498	C ₁₅ H ₁₀ O ₈ S	Deglycosylation+ isomerization+sulfation+ hydroxylation+ dehydrogenation	U
M8	10.27	333.00745	333.00707	1.13	253.05063	C ₁₅ H ₁₀ O ₇ S	Deglycosylation+dehydrogenation+sulfation	B
M9	19.55	333.00745	333.00717	0.84	253.05045	C ₁₅ H ₁₀ O ₇ S	Deglycosylation+dehydrogenation+sulfation	U
M10	21.50	333.00745	333.00740	0.15	253.05063	C ₁₅ H ₁₀ O ₇ S	Deglycosylation+dehydrogenation+sulfation	P
M11	8.13	429.08272	429.08270	0.05	253.05069	C ₂₁ H ₁₈ O ₁₀	Deglycosylation+dehydrogenation+glucuronidation	U, P
M12	9.91	429.08272	429.08270	0.05	253.05056	C ₂₁ H ₁₈ O ₁₀	Deglycosylation+dehydrogenation+glucuronidation	U
M20	23.56	365.07005	365.06969	0.97	–	C ₁₇ H ₁₈ O ₇ S	Deglycosylation+ isomerization+sulfation+ hydrogenation+ methylation	U
M32	16.33	447.12967	447.12953	0.31	271.06026	C ₂₂ H ₂₄ O ₁₀	Deglycosylation+ isomerization+glucuronidation+ methylation+ hydrogenation	U
M33	17.63	447.12967	447.12952	0.33	271.06027	C ₂₂ H ₂₄ O ₁₀	Deglycosylation+ isomerization+glucuronidation+ methylation+ hydrogenation	U
M51	21.11	414.97991	414.97975	0.39	255.06593	C ₁₅ H ₁₂ O ₁₀ S ₂	Deglycosylation+ isomerization+sulfation	U
M52	11.18	351.01801	351.01794	0.21	271.06028, 255.06542 135.53017	C ₁₅ H ₁₂ O ₈ S	Deglycosylation+ isomerization+sulfation+ hydroxylation	U
M53	20.02	351.01801	351.01784	0.49	271.06023, 255.06541 135.53011	C ₁₅ H ₁₂ O ₈ S	Deglycosylation+ isomerization+sulfation+ hydroxylation	U

M54	25.68	351.01801	351.01798	0.09	271.06040, 255.06549	135.53018	C ₁₅ H ₁₂ O ₈ S	Deglycosylation+ isomerization+sulfation+ hydroxylation	U
M55	28.82	351.01801	351.01769	0.90	271.06020, 255.06540	135.53014	C ₁₅ H ₁₂ O ₈ S	Deglycosylation+ isomerization+sulfation+ hydroxylation	U
M56	20.71	365.03366	365.03344	0.61	285.07632		C ₁₆ H ₁₄ O ₈ S	Deglycosylation+ isomerization+sulfation+ hydroxylation+ methylation	U
M57	23.04	365.03366	365.03339	0.75	285.07637		C ₁₆ H ₁₄ O ₈ S	Deglycosylation+ isomerization+sulfation+ hydroxylation+ methylation	U
M58	28.57	365.03366	365.03310	1.54	285.07645		C ₁₆ H ₁₄ O ₈ S	Deglycosylation+ isomerization+sulfation+ hydroxylation+ methylation	U
M70	2.79	609.14611	609.14646	-0.57	–		C ₂₇ H ₃₀ O ₁₆	Deglycosylation+ isomerization+glucuronidation+ hydrogenation	U
M71	12.82	609.14611	609.14551	0.99	–		C ₂₇ H ₃₀ O ₁₆	Deglycosylation+ isomerization+glucuronidation+ hydrogenation	U
M72	19.24	445.11402	445.11379	0.52	269.04459		C ₂₂ H ₂₂ O ₁₀	Deglycosylation+ isomerization+glucuronidation+ methylation	U
M73	3.29	447.09329	447.09309	0.43	271.06024, 255.06553	135.53028	C ₂₁ H ₂₀ O ₁₁	Deglycosylation+ isomerization+glucuronidation+ hydroxylation	U, B
M74	15.82	447.09329	447.09300	0.64	271.06027, 255.06552	135.53045	C ₂₁ H ₂₀ O ₁₁	Deglycosylation+ isomerization+glucuronidation+ hydroxylation	U, P
M75	14.76	579.17193	579.17295	-1.76	–		C ₂₇ H ₃₂ O ₁₄	hexose	P
M76	21.94	401.08784	401.08772	0.22	–		C ₂₀ H ₁₈ O ₉	Deglycosylation+dehydrogenation+pentaose	P

P, U, B and F represent rat plasma, urine, bile and feces samples, respectively.

“–” represent that MS/MS data of this metabolite was not detected.