

Physiology-based pharmacokinetic study on 18 β -glycyrrhetic acid mono-glucuronide (GAMG) prior to glycyrrhizin in rats

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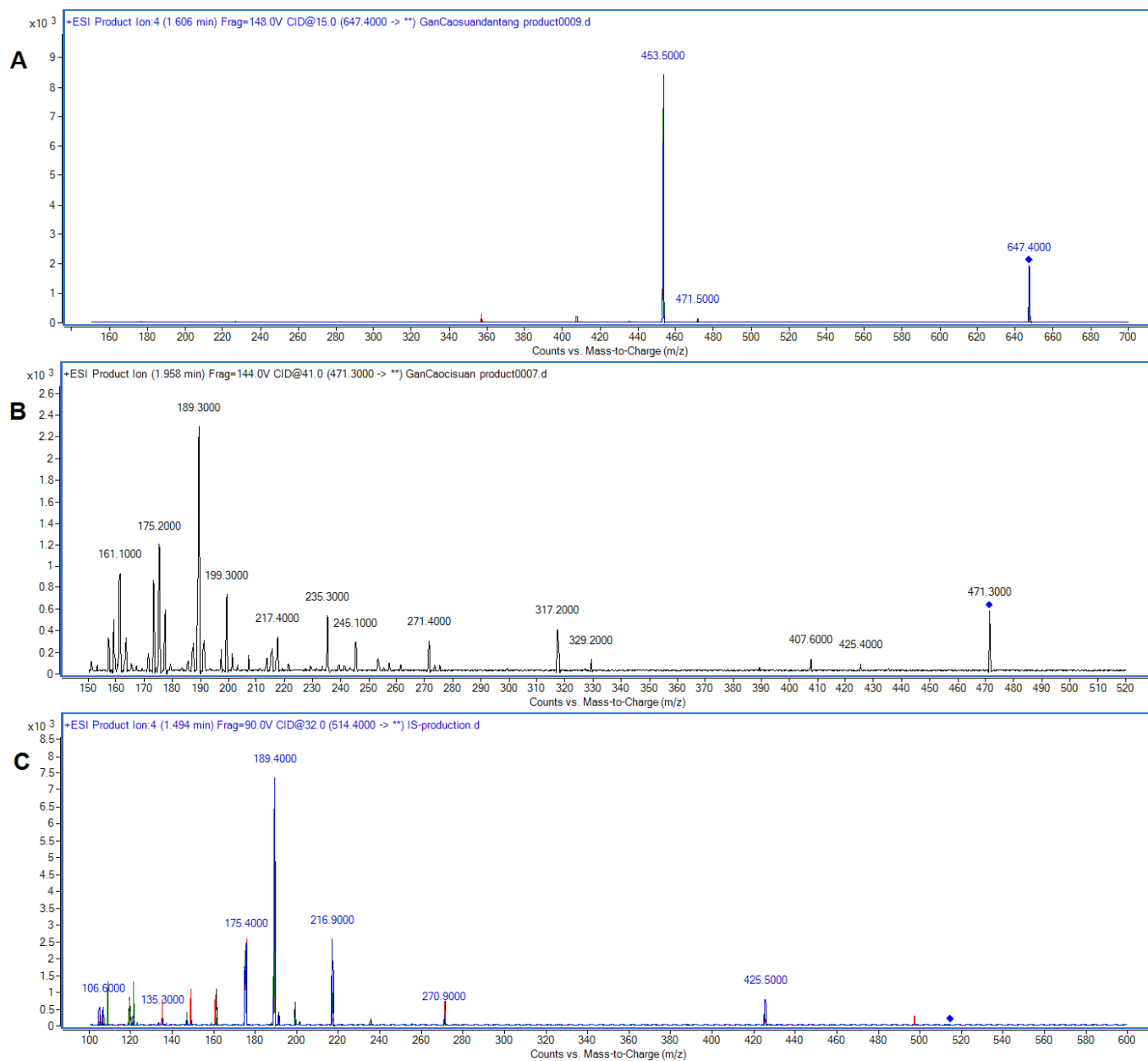


Figure S1. Total ion current of product ions for each analyte (A: GAM; B: GA; C: IS).

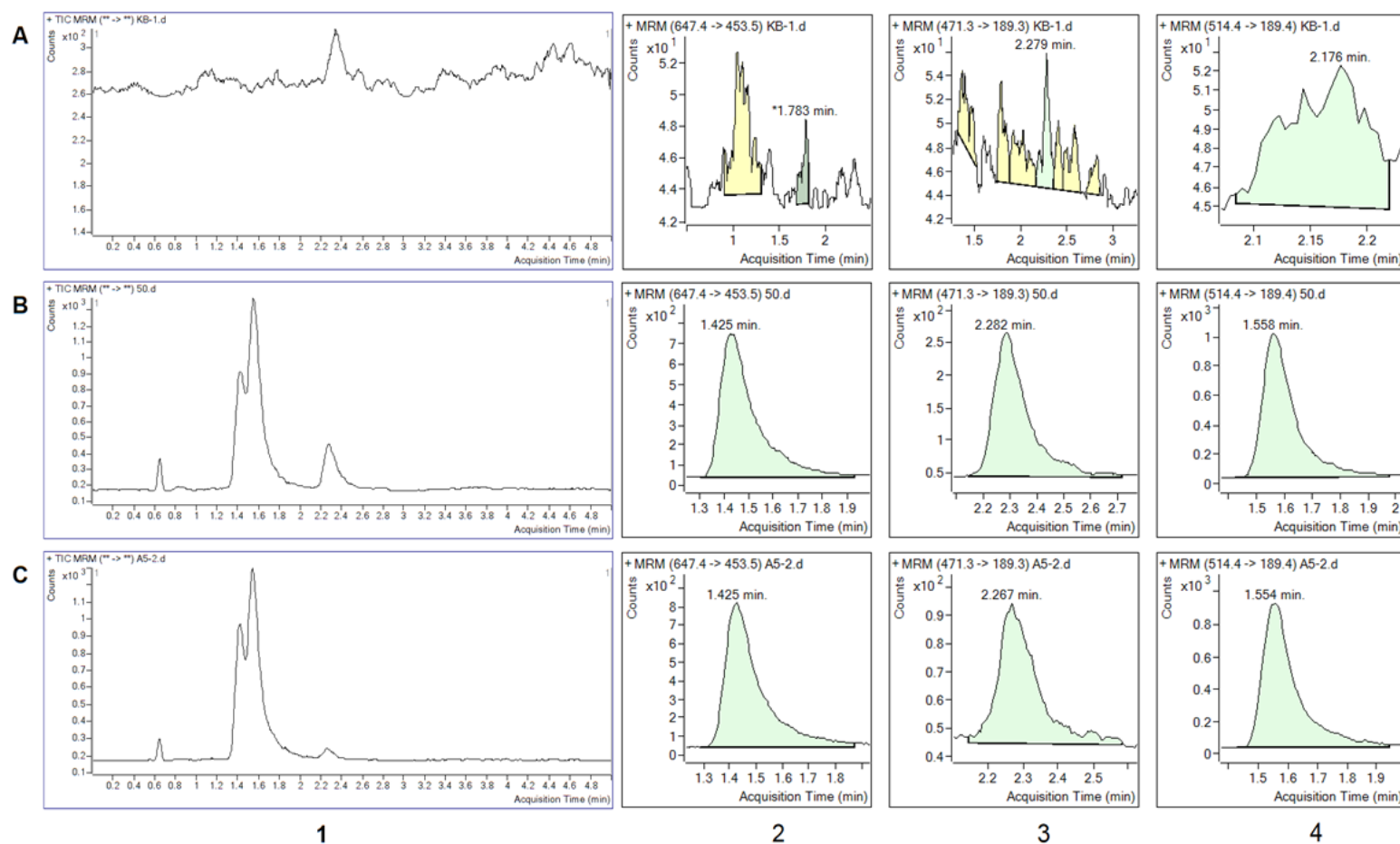


Figure S2. Specific chromatograms of each component in rat plasma. **A:** blank plasma sample; **B:** blank rat plasma added of standard references (GAMG 50 ng/mL, GA 50 ng/mL, IS 50 ng/mL); **C:** rat plasma sample obtained 0.25 h after ig 7.5 mg/kg GAMG. (1: Total ion current diagram; 2: GAMG; 3: GA; 4: IS).

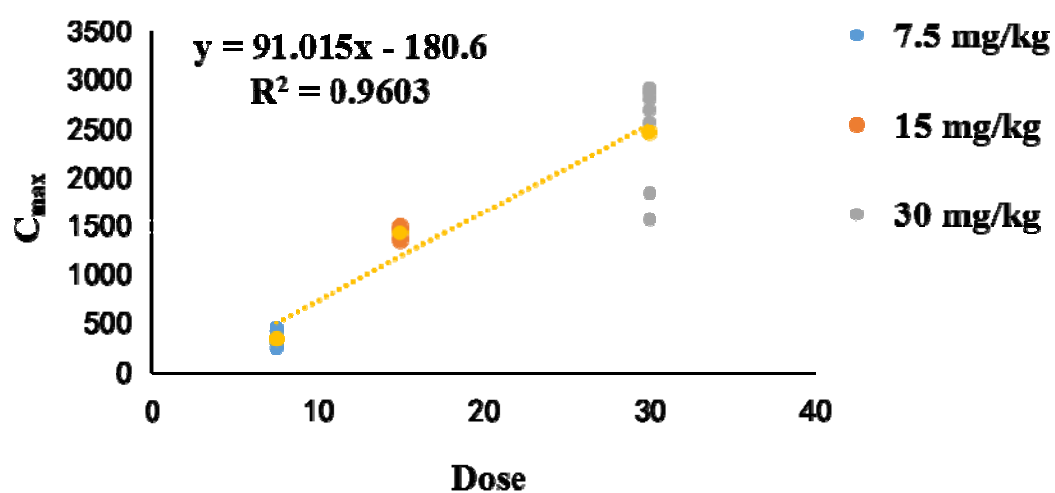


Figure S3. Linear relationship between GAMG dose and C_{max} .

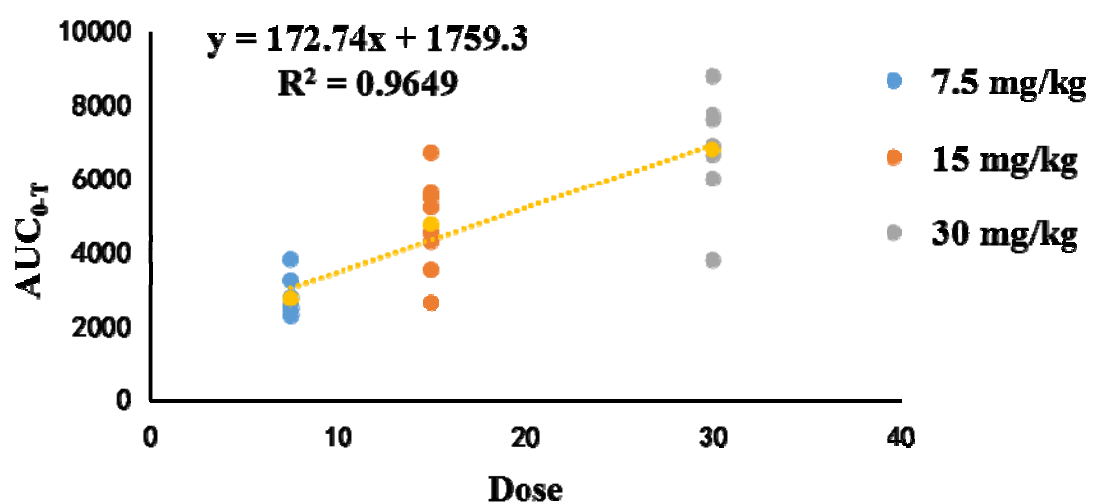


Figure S4. Linear relationship between GAMG dose and AUC_{0-T} .

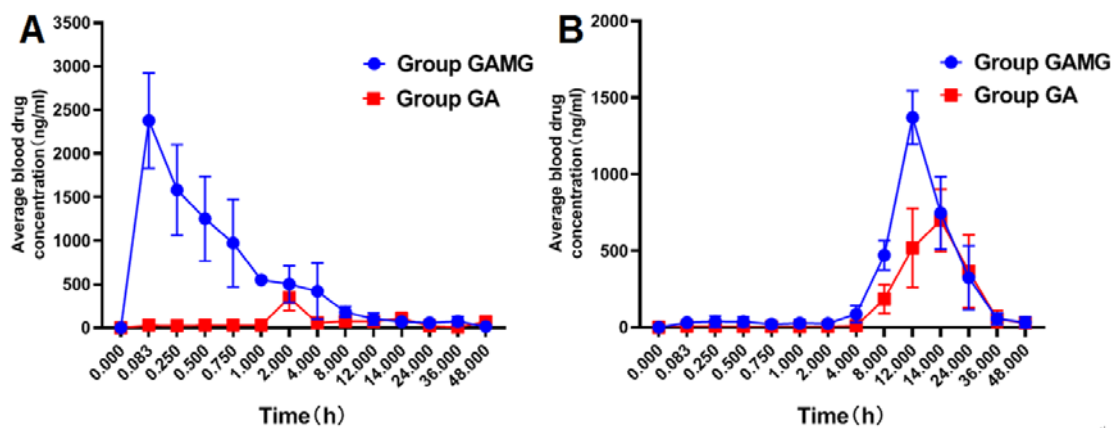


Figure S5. Average plasma concentration-time curve of each analyte (A: GAMG; B: GA) after ig two groups of rats (n = 6).

Table S1 Dilute reliable quality control samples (n = 5)

Analyte	Theoretical concentration (ng/mL)	Mean measure concentration (ng/mL)	RSD (%)	RE (%)
GAMG	40	40.93	0.85	2.08
	250	246.71	8.41	-1.32
	2500	2556.96	1.44	2.28
GA	40	37.25	7.62	-6.88
	250	238.56	3.84	-4.58
	500	538.94	2.65	7.89

Table S2 Pharmacokinetic parameters of GAMG after intragastric administration of three dose groups of GAMG in rats.

Group	Pharmacokinetic parameters	Female (n = 4, mean \pm SD)	Male (n = 4, mean \pm SD)	Total (n = 8, mean \pm SD)
Low dose group	C_{\max} (ng/mL)	336.45 \pm 57.93	346.86 \pm 111.70	341.65 \pm 82.56
	T_{\max} (h)	0.083 \pm 0.00	0.083 \pm 0.00	0.083 \pm 0.00
	$T_{1/2}$ (h)	19.73 \pm 4.57	17.38 \pm 7.32	18.56 \pm 5.79
	AUC _{0-T} (mg/L*h)	2526.84 \pm 211.48	3012.39 \pm 665.19	2769.61 \pm 525.51
	MRT _{0-T} (h)	17.36 \pm 1.92	15.32 \pm 3.74	16.34 \pm 2.96
	V_d (mL/kg)	92.93 \pm 31.06	94.70 \pm 40.13	93.82 \pm 33.23
	CL (mL/h/kg)	2.98 \pm 0.24	2.58 \pm 0.55	2.78 \pm 0.45
Medium dose group	C_{\max} (ng/mL)	1416.09 \pm 70.04	1434.21 \pm 61.24	1425.15 \pm 61.67
	T_{\max} (h)	0.083 \pm 0.00	0.083 \pm 0.00	0.083 \pm 0.00
	$T_{1/2}$ (h)	15.30 \pm 0.73	16.71 \pm 7.87	16.00 \pm 5.23
	AUC _{0-T} (mg/L*h)	5610.41 \pm 899.61	3945.85 \pm 1103.04	4778.13 \pm 1288.38
	MRT _{0-T} (h)	14.65 \pm 5.50	12.31 \pm 2.75	13.48 \pm 4.22
	V_d (mL/kg)	60.58 \pm 12.08	142.67 \pm 141.96	101.63 \pm 112.96
	CL (mL/h/kg)	2.73 \pm 0.44	4.05 \pm 1.20	3.39 \pm 1.20
High dose group	C_{\max} (ng/mL)	2454.84 \pm 42.46	2484.49 \pm 632.79	2469.66 \pm 502.01
	T_{\max} (h)	0.083 \pm 0.00	0.083 \pm 0.00	0.083 \pm 0.00
	$T_{1/2}$ (h)	12.73 \pm 4.89	16.71 \pm 7.87	14.72 \pm 6.43
	AUC _{0-T} (mg/L*h)	6769.46 \pm 2133.97	6828.23 \pm 713.66	6798.84 \pm 1473.40
	MRT _{0-T} (h)	11.85 \pm 3.06	12.31 \pm 2.75	12.08 \pm 2.70
	V_d (mL/kg)	73.96 \pm 33.08	109.72 \pm 61.99	91.84 \pm 49.81
	CL (mL/h/kg)	4.90 \pm 2.04	4.43 \pm 0.46	4.67 \pm 1.39

Table S3 Pharmacokinetic parameters of GAMG after intragastric administration of three dose groups of GA in rats.

Group	Pharmacokinetic parameters	Female (n = 4, mean \pm SD)	Male (n = 4, mean \pm SD)	Total (n = 8, mean \pm SD)
Low dose group	C_{\max} (ng/mL)	352.45 \pm 121.84	384.61 \pm 91.70	368.53 \pm 101.30
	T_{\max} (h)	10.00 \pm 2.31	10.50 \pm 3.00	10.25 \pm 2.49
	$T_{1/2}$ (h)	6.10 \pm 2.25	7.00 \pm 1.96	6.54 \pm 2.01
	AUC_{0-T} (mg/L*h)	3951.21 \pm 956.06	4327.73 \pm 1012.36	4139.47 \pm 933.53
	MRT_{0-T} (h)	15.38 \pm 2.54	16.40 \pm 1.06	15.89 \pm 1.88
	V_d (mL/kg)	71.01 \pm 37.22	77.13 \pm 43.77	74.07 \pm 37.76
	CL (mL/h/kg)	7.94 \pm 1.90	7.27 \pm 1.92	7.60 \pm 1.80
Medium dose group	C_{\max} (ng/mL)	688.87 \pm 90.18	784.98 \pm 115.60	736.93 \pm 107.06
	T_{\max} (h)	10.00 \pm 2.31	12.00 \pm 0.00	11.00 \pm 1.85
	$T_{1/2}$ (h)	6.92 \pm 1.04	6.72 \pm 0.86	6.82 \pm 0.89
	AUC_{0-T} (mg/L*h)	7637.86 \pm 1172.14	6342.56 \pm 1094.78	6990.21 \pm 1257.71
	MRT_{0-T} (h)	13.58 \pm 0.96	13.80 \pm 0.69	13.69 \pm 0.78
	V_d (mL/kg)	40.53 \pm 12.22	46.77 \pm 3.14	43.65 \pm 8.90
	CL (mL/h/kg)	4.00 \pm 0.65	4.84 \pm 0.62	4.42 \pm 0.82
High dose group	C_{\max} (ng/mL)	1403.44 \pm 98.14	1453.97 \pm 59.30	1428.70 \pm 79.78
	T_{\max} (h)	12.50 \pm 1.00	12.00 \pm 0.00	12.25 \pm 0.71
	$T_{1/2}$ (h)	10.23 \pm 5.43	5.36 \pm 0.54	7.79 \pm 4.42
	AUC_{0-T} (mg/L*h)	14463.37 \pm 5415.07	15789.13 \pm 2952.52	15126.25 \pm 4099.42
	MRT_{0-T} (h)	16.07 \pm 1.23	15.56 \pm 0.72	15.82 \pm 0.97
	V_d (mL/kg)	41.82 \pm 42.73	15.22 \pm 4.13	28.52 \pm 31.50
	CL (mL/h/kg)	2.38 \pm 1.13	1.95 \pm 0.36	2.17 \pm 0.81

Table S4 Pharmacokinetic parameters of GAMG after ig for two groups of rats (n = 6)

PK parameters	GL group (n = 6, mean \pm SD)	GAMG group (n = 6, mean \pm SD)
C_{\max} (ng/mL)	346.03 \pm 145.13	2377.57 \pm 547.40
T_{\max} (h)	2.00 \pm 0.00	0.083 \pm 0.00
$T_{1/2}$ (h)	8.18 \pm 2.48	15.73 \pm 7.26
AUC _{0-T} (mg/L*h)	459.32 \pm 80.81	6625.54 \pm 1680.70
MRT _{0-T} (h)	17.54 \pm 2.81	11.22 \pm 2.58
V_d (mL/kg)	133.15 \pm 41.06	99.25 \pm 56.43
CL (mL/h/kg)	11.30 \pm 1.93	4.85 \pm 1.59

Table S5 Pharmacokinetic parameters of GA after two groups of rats (n = 6)

PK parameters	GL group (n = 6, mean \pm SD)	GAMG group (n = 6, mean \pm SD)
C_{\max} (ng/mL)	747.08 \pm 236.85	1412.58 \pm 80.83
T_{\max} (h)	13.67 \pm 0.82	12.33 \pm 0.82
$T_{1/2}$ (h)	7.54 \pm 2.86	8.48 \pm 5.00
AUC _{0-T} (mg/L*h)	11598.49 \pm 4496.08	15252.54 \pm 4661.22
MRT _{0-T} (h)	18.14 \pm 2.35	15.99 \pm 1.07
V_d (mL/kg)	32.06 \pm 15.70	32.26 \pm 36.29
CL (mL/h/kg)	3.00 \pm 1.38	2.20 \pm 0.94

Table S6 Concentration distribution results of GAMG and GA in various tissues (n = 6)

tissue	Analyte	Con. (µg/g)				
		0	0.5 h	1 h	4 h	12 h
heart	GAMG	0	0.657 ± 0.231	0.135 ± 0.042	0.086 ± 0.023	0.606 ± 0.278
	GA	0	0.049 ± 0.014	0.027 ± 0.004	0.086 ± 0.023	0.158 ± 0.045
liver	GAMG	0	1.946 ± 0.499	0.800 ± 0.291	0.096 ± 0.046	0.245 ± 0.077
	GA	0	0.089 ± 0.013	0.054 ± 0.016	0.142 ± 0.072	0.332 ± 0.060
spleen	GAMG	0	3.167 ± 0.765	0.386 ± 0.111	0.743 ± 0.228	0.894 ± 0.130
	GA	0	0.087 ± 0.039	0.012 ± 0.008	0.018 ± 0.008	0.052 ± 0.019
lung	GAMG	0	1.035 ± 0.083	0.869 ± 0.249	0.436 ± 0.139	1.942 ± 0.227
	GA	0	0.072 ± 0.018	0.027 ± 0.008	0.259 ± 0.069	0.705 ± 0.134
kidney	GAMG	0	3.859 ± 0.537	0.867 ± 0.151	0.271 ± 0.063	1.136 ± 0.153
	GA	0	0.054 ± 0.033	0.014 ± 0.005	0.193 ± 0.085	0.479 ± 0.124
brain	GAMG	0	1.012 ± 0.142	0.481 ± 0.105	0.259 ± 0.099	0.288 ± 0.033
	GA	0	0	0	0	0
Small intestine	GAMG	0	2.509 ± 0.729	5.634 ± 0.165	0.493 ± 0.181	0.164 ± 0.045
	GA	0	0.032 ± 0.029	0.108 ± 0.104	0.070 ± 0.093	0.032 ± 0.023