

Supplementary Materials

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Pharmacokinetics, tissue distribution, metabolism, and excretion of naringin in aged rats

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Table S1. Results of method validation for the determination of naringin (NG), naringenin (NE), hesperetin (HE), apigenin (AE), hippuric acid (HA), 4-hydroxybenzoic acid (4HBA), and 3-(4'-hydroxyphenyl)propionic acid (4HPPA) in biological samples.

Matrix	Compounds	Calibration curve range (ng/mL)	Linearity equations	r	Within-run precisions (%) (n=6)		Between-run precisions	Coefficient of variation of matrix factors (%) (n=6)	
					LLOQ ^a	L, M, H ^b	(%) (n=18)	L	H
Plasma	NG	4.820~1928	Y=0.0743*X+2.057E-005	0.9979	10.6~17.2	5.2~8.6	6.2~14.8	2.9	0.8
	NE	5.450~2180	Y=0.0881*X-8.353E-005	0.9986	5.8~13.1	3.0~14.2	4.6~12.9	4.3	2.2
Stomach	NG	9.640~3856	Y=0.1404*X-1.248E-004	0.9950	4.2~8.5	3.0~9.5	3.9~7.0	11.9	9.5
	NE	5.450~2180	Y=0.3253*X-1.504E-004	0.9944	3.4~7.9	2.1~6.2	2.9~6.3	10.4	12.7
Intestines	NG	9.640~3856	Y=0.2757*X-7.658E-004	0.9939	4.3~10.6	0.6~3.1	2.3~7.9	2.1	13.1
	NE	5.450~2180	Y=0.2724*X-8.390E-005	0.9982	5.3~11.3	2.1~5.9	3.5~8.2	13.8	9.9
Liver	NG	4.820~964.0	Y=0.1958*X+9.865E-004	0.9977	9.4~12.4	1.3~10.2	5.9~11.0	5.4	8.7
	NE	5.450~1090	Y=0.1849*X-2.139E-004	0.9959	8.8~11.9;	2.9~12.9	8.6~11.4	3.7	8.5
Kidney	NG	2.410~482.0	Y=0.5159*X-0.0011	0.9968	11.6~14.9	2.1~12.0	2.4~13.9	5.4	3.3
	NE	5.450~1090	Y=0.7359*X-0.0048	0.9926	7.2~15.1	2.3~9.4	3.7~10.9	9.4	7.9
Trachea	NG	4.820~482.0	Y=0.0484*X-4.888E-005	0.9951	11.0~14.8	2.8~13.0	8.7~14.7	8.7	4.2
	NE	2.725~272.5	Y=0.3431*X-0.0012	0.9980	1.9~9.4	7.8~12.3	7.3~11.1	9.0	12.8
Lung	NG	2.410~241.0	Y=0.1125*X-8.2494E-004	0.9961	7.0~11.1	1.9~10.0	3.0~11.0	4.4	2.6
	NE	2.725~272.5	Y=0.4211*X-0.0012	0.9986	5.1~13.5	2.3~8.1	4.1~10.0	13.6	13.8
Heart	NG	2.410~241.0	Y=0.1399*X+5.7987E-004	0.9947	11.1~13.9	2.3~13.7	6.7~11.9	5.4	1.4
	NE	2.725~272.5	Y=0.1780*X+0.0010	0.9965	6.2~11.1	5.5~10.0	7.2~10.6	9.2	10.6
Spleen	NG	2.410~241.0	Y=0.1361*X-6.2228E-005	0.9989	9.6~18.3	2.0~10.6	3.0~14.5	4.0	2.0
	NE	2.725~272.5	Y=0.4076*X-9.9717E-004	0.9953	6.1~9.2	3.2~9.7	5.4~8.2	13.2	14.8
Muscle	NG	2.410~241.0	Y=0.1143*X+4.4749E-004	0.9954	6.8~19.4	6.1~12.0	8.1~14.8	1.5	1.5
	NE	2.725~272.5	Y=0.4584*X-0.0016	0.9962	7.8~10.8	1.9~9.2	5.1~8.9	4.6	2.5

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Fat	NG	2.410~241.0	$Y=0.0188*X+1.0842E-004$	0.9987	10.5~14.5	2.9~8.8	5.3~12.7	4.4	7.7
	NE	2.725~272.5	$Y=0.0132*X-2.8570E-005$	0.9960	4.3~18.9	2.7~10.3	3.4~12.2	14.3	13.0
Brain	NG	2.410~241.0	$Y=0.1334*X+5.1398E-004$	0.9950	6.6~17.2	3.5~11.2	7.6~12.6	2.4	0.3
	NE	2.725~272.5	$Y=0.3706*X+2.1430E-005$	0.9976	5.9~18.3	1.1~11.9	3.2~14.1	11.6	4.6
Urine	NG	2.470~988.0	$Y=129.5*X+303.6$	0.9993	10.1~12.7	1.8~11.2	7.1~11.0	9.0	5.8
	NE	26.80~10720	$Y=115.5*X-758.0$	0.9989	4.6~6.0	0.9~6.4	3.6~5.5	9.4	7.4
	HE	2.427~970.9	$Y=24.70*X+4.700$	0.9986	6.8~12.2	2.5~14.6	5.9~12.3	5.6	5.4
	AE	12.46~4986	$Y=39.20*X+79.00$	0.9995	6.4~9.1	1.3~7.5	2.3~8.2	3.4	5.8
	HA	5575~55750	$Y=2621.5*X+54215.3$	0.9966	5.9~10.3	2.2~10.0	4.9~9.7	13.8	8.2
	4HBA	1087~10870	$Y=2368.3*X+2391.1$	0.9979	3.6~11.5	2.7~8.9	5.5~8.9	6.3	9.7
	4HPPA	9996~99960	$Y=911.5*X+25749.8$	0.9960	5.2~10.9	2.4~9.9	5.2~8.2	5.9	8.6
Feces	NG	1.976~197.6	$Y=9.732E-006*X+1.031E-004$	0.9989	8.2~12.0	4.7~11.0	8.0~11.4	8.9	5.8
	NE	2.144~214.4	$Y=1.406E-004*X-9.754E-005$	0.9960	4.1~14.3	1.7~9.3	3.2~9.0	4.6	3.0
	HE	1.942~194.2	$Y=1.441E-005*X-9.553E-006$	0.9989	9.0~9.7	2.5~11.1	3.9~10.0	13.3	3.3
	AE	0.9972~99.72	$Y=4.950E-005*X+1.520E-005$	0.9980	8.8~10.0	2.5~10.9	5.4~10.2	8.3	2.6
	HA	278.8~2788	$Y=0.0085*X+3.044E-004$	0.9985	4.3~10.2	1.7~10.4	5.7~7.9	1.5	2.2
	4HBA	271.8~2718	$Y=0.0075*X+2.078E-004$	0.9954	4.8~10.1	3.6~10.2	5.6~8.6	5.3	3.5
	4HPPA	2499~24990	$Y=0.0032*X+0.0167$	0.9932	9.0~10.2	3.4~8.7	6.6~9.9	2.9	5.0

^a LLOQ, lower limit of quantification.

^b L, M, H represent low, middle, high QC concentration levels, respectively.

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Table S2. AUC, C_{max} and T_{max} for naringin and total naringenin in tissues after a single oral administration of 42 mg/kg naringin to aged rats.

Tissues	Naringin			Total naringenin		
	AUC (ng*h/g)	C _{max} (ng/g)	T _{max} (h)	AUC (ng*h/g)	C _{max} (ng/g)	T _{max} (h)
Stomach	658476	820478	0.25	111641	38431	0.25
Duodenum	840117	1232198	0.25	473033	70936	6
Jejunum	2404138	1059446	1	1251818	182364	6
Ileum	3761105	1003811	1	1490177	149457	6
Colon	895386	214840	3	411298	56032	3
Liver	5879	7087	0.25	121958	21423	6
Kidney	5286	7691	0.25	65837	12706	6
Lung	161811	108925	1	16294	2538	1
Trachea	80225	52876	1	13826	3623	1
Heart	1070	211.9	0.25	13530	1426	6
Fat	1589	159.9	10	4308	490.3	6
Spleen	1152	181.0	0.25	3163	479.7	6
Muscle	1799	358.9	0.25	2306	291.3	6
Brain	1040	222.9	10	913.0	75.9	6

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Table S3. UFLC-Q-TOF-MS/MS based identifications of flavonoid metabolites urine and feces samples collected 0-48 h after a single oral administration of naringin in aged rats.

No.	Identified metabolites	Formula	RT (min)	[M-H] ⁻ (Error, ppm)	Fragment ions in negative mode ^a	Source
Parent drug	Naringin ^b	C ₂₇ H ₃₂ O ₁₄	11.4	579.1717 (-0.4)	459.1196[M-H-C ₈ H ₈ O] ⁻ , 313.0713[M-H-C ₈ H ₈ O-Rha] ⁻ , 271.0601[M-H-Rha-Glc] ⁻ , 151.0024[M-H-Rha-Glc-C ₈ H ₈ O] ⁻	Urine, Feces
M1	Naringenin ^b	C ₁₅ H ₁₂ O ₅	13.7	271.0617 (1.8)	177.0202[M-H-C ₆ H ₆ O] ⁻ , 151.0043[M-H-C ₈ H ₈ O] ⁻ , 119.0512[M-H-C ₇ H ₄ O ₄] ⁻ , 107.0150[M-H-C ₈ H ₈ O-CO ₂] ⁻ , 93.0366[M-H-C ₉ H ₆ O ₄] ⁻ , 83.0147	Urine, Feces
M2	Naringenin-5- <i>O</i> -glucuronide	C ₂₁ H ₂₀ O ₁₁	10.7	447.0932 (-0.2)	271.0610[M-H-GlcUA] ⁻ , 175.0251[M-H-NE] ⁻ , 151.0037[M-H-GlcUA-C ₈ H ₈ O] ⁻ , 113.0259[M-H-NE-CO ₂ -H ₂ O] ⁻	Urine
M3	Naringenin-7- <i>O</i> -glucuronide ^b	C ₂₁ H ₂₀ O ₁₁	11.5	447.0941 (1.8)	271.0611[M-H-GlcUA] ⁻ , 227.0715, 177.0191[M-H-GlcUA-C ₆ H ₆ O] ⁻ , 175.0239[M-H-NE] ⁻ , 151.0034[M-H-GlcUA-C ₈ H ₈ O] ⁻ , 119.0509[M-H-GlcUA-C ₇ H ₄ O ₄] ⁻ , 113.0251[M-H-NE-CO ₂ -H ₂ O] ⁻ , 85.0318[M-H-NE-CO ₂ -H ₂ O-CO] ⁻	Urine
M4	Naringenin-4'- <i>O</i> -glucuronide ^b	C ₂₁ H ₂₀ O ₁₁	11.7	447.0942 (2.1)	271.0614[M-H-GlcUA] ⁻ , 177.0197[M-H-GlcUA-C ₆ H ₆ O] ⁻ , 175.0252[M-H-NE] ⁻ , 151.0046[M-H-GlcUA-C ₈ H ₈ O] ⁻ , 119.0516[M-H-GlcUA-C ₇ H ₄ O ₄] ⁻ , 113.0258[M-H-NE-CO ₂ -H ₂ O] ⁻ , 85.0320[M-H-NE-CO ₂ -H ₂ O-CO] ⁻	Urine
M5	Naringenin-4',7- <i>O</i> -diglucuronide	C ₂₇ H ₂₈ O ₁₇	8.7	623.1247 (-1.2)	447.0915[M-H-GlcUA] ⁻ , 313.0691[M-H-GlcUA-C ₄ H ₆ O ₅] ⁻ , 271.0600[M-H-2GlcUA] ⁻ , 175.0236[M-H-NE-GlcUA] ⁻ , 151.0033[M-H-2GlcUA-C ₈ H ₈ O] ⁻ , 113.0240[M-H-NE-GlcUA-CO ₂ -H ₂ O] ⁻ , 107.0143[M-H-2GlcUA-C ₈ H ₈ O-CO ₂] ⁻ , 85.0310[M-H-NE-GlcUA-CO ₂ -H ₂ O-CO] ⁻	Urine
M6	Naringenin-5,7- <i>O</i> -diglucuronide	C ₂₇ H ₂₈ O ₁₇	9.4	623.1257 (0.6)	447.0943[M-H-GlcUA] ⁻ , 271.0610[M-H-2GlcUA] ⁻ , 175.0223[M-H-NE-GlcUA] ⁻ , 151.0027[M-H-2GlcUA-C ₈ H ₈ O] ⁻ , 113.0224[M-H-NE-GlcUA-CO ₂ -H ₂ O] ⁻	Urine
M7	Naringenin-4',5- <i>O</i> -diglucuronide	C ₂₇ H ₂₈ O ₁₇	10.8	623.1240 (-2.2)	447.0939[M-H-GlcUA] ⁻ , 313.0705[M-H-GlcUA-C ₄ H ₆ O ₅] ⁻ , 271.0618[M-H-2GlcUA] ⁻ , 175.0244[M-H-NE-GlcUA] ⁻ , 151.0033[M-H-2GlcUA-C ₈ H ₈ O] ⁻ ,	Urine

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M8	Naringenin-4'- <i>O</i> -sulfate	C ₁₅ H ₁₂ O ₈ S	10.0	351.0181 (0.2)	113.0254[M-H-NE-GlcUA-CO ₂ -H ₂ O] ⁻ 271.0610[M-H-SO ₃] ⁻ , 177.0182[M-H-SO ₃ -C ₆ H ₆ O] ⁻ , 165.0180[M-H-SO ₃ - C ₇ H ₆ O] ⁻ , 151.0038[M-H-SO ₃ -C ₈ H ₈ O] ⁻ , 119.0510[M-H-SO ₃ -C ₇ H ₄ O ₄] ⁻ , 107.0158[M-H-SO ₃ -C ₈ H ₈ O-CO ₂] ⁻ , 93.0366[M-H-SO ₃ -C ₉ H ₆ O ₄] ⁻ , 83.0152	Urine
M9	Naringenin-7- <i>O</i> -sulfate	C ₁₅ H ₁₂ O ₈ S	12.1	351.0186 (1.7)	271.0608[M-H-SO ₃] ⁻ , 177.0185[M-H-SO ₃ -C ₆ H ₆ O] ⁻ , 151.0035[M-H-SO ₃ - C ₈ H ₈ O] ⁻ , 119.0508[M-H-SO ₃ -C ₇ H ₄ O ₄] ⁻ , 107.0150[M-H-SO ₃ -C ₈ H ₈ O-CO ₂] ⁻ , 93.0356[M-H-SO ₃ -C ₉ H ₆ O ₄] ⁻ , 83.0149	Urine
M10	Naringenin- <i>O</i> -disulfate	C ₁₅ H ₁₂ O ₁₁ S ₂	12.2	430.9744 (-1.0)	351.0169[M-H-SO ₃] ⁻ , 271.0599[M-H-2SO ₃] ⁻ , 177.0185[M-H-2SO ₃ - C ₆ H ₆ O] ⁻ , 151.0048[M-H-2SO ₃ -C ₈ H ₈ O] ⁻ , 119.0507[M-H-2SO ₃ -C ₇ H ₄ O ₄] ⁻ , 96.9621, 93.0341[M-H-2SO ₃ -C ₉ H ₆ O ₄] ⁻	Urine
M11	Naringenin- <i>O</i> -glucuronide- <i>O</i> -sulfate	C ₂₁ H ₂₀ O ₁₄ S	7.6	527.0483 (-3.3)	447.0929[M-H-SO ₃] ⁻ , 351.0202[M-H-GlcUA] ⁻ , 286.0708, 271.0599[M-H- SO ₃ -GlcUA] ⁻ , 175.0195[M-H-SO ₃ -NE] ⁻ , 151.0062[M-H-SO ₃ -GlcUA- C ₈ H ₈ O] ⁻ , 113.0226[M-H-SO ₃ -NE -CO ₂ -H ₂ O] ⁻ , 85.0328[M-H-SO ₃ -NE -CO ₂ - H ₂ O-CO] ⁻	Urine
M12	Naringenin- <i>O</i> -glucuronide- <i>O</i> -sulfate	C ₂₁ H ₂₀ O ₁₄ S	8.0	527.0491 (-1.9)	447.0923[M-H-SO ₃] ⁻ , 351.0170[M-H-GlcUA] ⁻ , 271.0604[M-H-SO ₃ - GlcUA] ⁻ , 177.0188[M-H-SO ₃ -GlcUA-C ₆ H ₆ O] ⁻ , 175.0236[M-H-SO ₃ -NE] ⁻ , 151.0022[M-H-SO ₃ -GlcUA-C ₈ H ₈ O] ⁻ , 113.0245[M-H-SO ₃ -NE -CO ₂ -H ₂ O] ⁻ , 96.9608, 85.0310[M-H-SO ₃ -NE -CO ₂ -H ₂ O-CO] ⁻	Urine
M13	Naringenin- <i>O</i> -glucuronide- <i>O</i> -sulfate	C ₂₁ H ₂₀ O ₁₄ S	8.9	527.0484 (-3.3)	447.0945[M-H-SO ₃] ⁻ , 351.0177[M-H-GlcUA] ⁻ , 313.0721[M-H-SO ₃ - C ₄ H ₆ O ₅] ⁻ , 271.0605[M-H-SO ₃ -GlcUA] ⁻ , 254.0707, 227.0710, 175.0243[M- H-SO ₃ -NE] ⁻ , 165.0182[M-H-SO ₃ -GlcUA-C ₇ H ₆ O] ⁻ , 151.0022[M-H-SO ₃ - GlcUA-C ₈ H ₈ O] ⁻ , 119.0502[M-H-SO ₃ -GlcUA-C ₇ H ₄ O ₄] ⁻ , 113.0243[M-H- SO ₃ -NE -CO ₂ -H ₂ O] ⁻ , 96.9606, 85.0334[M-H-SO ₃ -NE -CO ₂ -H ₂ O-CO] ⁻	Urine
M14	Naringenin- <i>O</i> -glucuronide- <i>O</i> -sulfate	C ₂₁ H ₂₀ O ₁₄ S	10.1	527.0486 (-2.9)	447.0936[M-H-SO ₃] ⁻ , 351.0183[M-H-GlcUA] ⁻ , 271.0611[M-H-SO ₃ - GlcUA] ⁻ , 175.0253[M-H-SO ₃ -NE] ⁻ , 151.0043[M-H-SO ₃ -GlcUA-C ₈ H ₈ O] ⁻ , 113.0258[M-H-SO ₃ -NE -CO ₂ -H ₂ O] ⁻ , 85.0324[M-H-SO ₃ -NE -CO ₂ -H ₂ O-	Urine

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					CO] ⁻	
M15	Naringenin- <i>O</i> -glucoside- <i>O</i> -glucuronide	C ₂₇ H ₃₀ O ₁₆	8.8	609.1456 (-0.8)	447.0935[M-H-Glc] ⁻ , 433.1141[M-H-GlcUA] ⁻ , 402.1669[M-H-Glc-COOH] ⁻ , 313.0712[M-H-Glc-C ₄ H ₆ O ₅] ⁻ , 271.0594[M-H-Glc-GlcUA] ⁻ , 151.0000[M-H-Glc-GlcUA-C ₈ H ₈ O] ⁻ , 113.0237[M-H-Glc-NE-CO ₂ -H ₂ O] ⁻	Urine
M16	Naringenin- <i>O</i> -glucoside- <i>O</i> -sulfate	C ₂₁ H ₂₂ O ₁₃ S	9.0	513.0710 (0.4)	433.1135[M-H-SO ₃] ⁻ , 358.9718, 313.0564[M-H-SO ₃ -C ₄ H ₈ O ₄] ⁻ , 271.0600[M-H-SO ₃ -Glc] ⁻ , 151.0018[M-H-SO ₃ -Glc-C ₈ H ₈ O] ⁻ , 119.0491[M-H-SO ₃ -Glc-C ₇ H ₄ O ₄] ⁻	Urine
M17	Naringenin- <i>O</i> -glucoside- <i>O</i> -sulfate	C ₂₁ H ₂₂ O ₁₃ S	9.4	513.0703 (-1.1)	433.1145[M-H-SO ₃] ⁻ , 313.0560[M-H-SO ₃ -C ₄ H ₈ O ₄] ⁻ , 271.0603[M-H-SO ₃ -Glc] ⁻ , 177.0197[M-H-SO ₃ -Glc-C ₆ H ₆ O] ⁻ , 151.0030[M-H-SO ₃ -Glc-C ₈ H ₈ O] ⁻ , 119.0500[M-H-SO ₃ -Glc-C ₇ H ₄ O ₄] ⁻ , 107.0137[M-H-SO ₃ -Glc-C ₈ H ₈ O-CO ₂] ⁻	Urine
M18	Methylnaringenin- <i>O</i> -glucuronide	C ₂₂ H ₂₂ O ₁₁	13.5	461.1087 (-0.4)	443.1747[M-H-H ₂ O] ⁻ , 285.0765[M-H-GlcUA] ⁻ , 175.0232[M-H-MNE] ⁻ , 164.0098, 151.0022[M-H-GlcUA-C ₉ H ₁₀ O] ⁻ , 113.0248[M-H-MNE-CO ₂ -H ₂ O] ⁻ , 96.9612, 85.0326[M-H-MNE-CO ₂ -H ₂ O-CO] ⁻	Urine
M19	Apiferol	C ₁₅ H ₁₄ O ₅	13.8	273.0765 (-1.2)	167.0352, 153.0089[M-H-C ₈ H ₈ O] ⁻ , 123.0448, 119.0504[M-H-C ₇ H ₆ O ₄] ⁻ , 93.0345[M-H-C ₉ H ₈ O ₄] ⁻	Urine
M20	Apigenin ^b	C ₁₅ H ₁₀ O ₅	15.0	269.0455 (-0.3)	251.1606[M-H-H ₂ O] ⁻ , 225.1405, 151.0065[M-H-C ₈ H ₆ O] ⁻ , 117.0306[M-H-C ₇ H ₄ O ₄] ⁻ , 98.9536[M-H-C ₇ H ₄ O ₄ -H ₂ O] ⁻	Urine, Feces
M21	Apigenin- <i>O</i> -glucuronide	C ₂₁ H ₁₈ O ₁₁	11.1	445.0772 (-1.0)	269.0440[M-H-GlcUA] ⁻ , 175.0234[M-H-AE] ⁻ , 113.0242[M-H-AE-CO ₂ -H ₂ O] ⁻ , 96.9604, 85.0321[M-H-AE-CO ₂ -H ₂ O-CO] ⁻	Urine
M22	Apigenin- <i>O</i> -glucuronide	C ₂₁ H ₁₈ O ₁₁	12.3	445.0778 (0.3)	269.0449[M-H-GlcUA] ⁻ , 175.0241[M-H-AE] ⁻ , 113.0240[M-H-AE-CO ₂ -H ₂ O] ⁻ , 96.9603, 85.0316[M-H-AE-CO ₂ -H ₂ O-CO] ⁻	Urine
M23	Apigenin- <i>O</i> -sulfate	C ₁₅ H ₁₀ O ₈ S	13.4	349.0024 (0.1)	269.0445[M-H-SO ₃] ⁻ , 117.0350[M-H-SO ₃ -C ₇ H ₄ O ₄] ⁻ , 96.9609	Urine
M24	Eriodictyol ^b	C ₁₅ H ₁₂ O ₆	12.7	287.0558 (-1.2)	225.0700, 201.1115, 175.0711, 151.0041[M-H-C ₈ H ₈ O ₂] ⁻ , 135.0456[M-H-C ₇ H ₄ O ₄] ⁻ , 107.0130[M-H-C ₈ H ₈ O ₂ -CO ₂] ⁻	Urine, Feces
M25	Eriodictyol- <i>O</i> -glucuronide	C ₂₁ H ₂₀ O ₁₂	10.5	463.0865	383.1953, 287.0555[M-H-GlcUA] ⁻ , 175.0246[M-H-EY] ⁻ , 151.0033[M-H-	Urine

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				(-3.7)	GlcUA-C ₈ H ₈ O ₂] ⁻ , 135.0448[M-H-GlcUA-C ₇ H ₄ O ₄] ⁻ , 113.0251[M-H-EY-CO ₂ -H ₂ O] ⁻ , 107.0144[M-H-GlcUA-C ₈ H ₈ O ₂ -CO ₂] ⁻ , 85.0321[M-H-EY-CO ₂ -H ₂ O-CO] ⁻	
M26	Eriodictyol- <i>O</i> -glucuronide	C ₂₁ H ₂₀ O ₁₂	11.5	463.0884	287.0528[M-H-GlcUA] ⁻ , 151.0024[M-H-GlcUA-C ₈ H ₈ O ₂] ⁻ , 113.0260[M-H-EY-CO ₂ -H ₂ O] ⁻	Urine
M27	Eriodictyol- <i>O</i> -sulfate	C ₁₅ H ₁₂ O ₉ S	11.2	367.0127	287.0551[M-H-SO ₃] ⁻ , 151.0038[M-H-SO ₃ -C ₈ H ₈ O ₂] ⁻ , 135.0419[M-H-SO ₃ -C ₇ H ₄ O ₄] ⁻ , 96.9621	Urine
M28	Eriodictyol- <i>O</i> -sulfate	C ₁₅ H ₁₂ O ₉ S	12.3	367.0127	287.0542[M-H-SO ₃] ⁻ , 151.0023[M-H-SO ₃ -C ₈ H ₈ O ₂] ⁻ , 135.0442[M-H-SO ₃ -C ₇ H ₄ O ₄] ⁻ , 107.0165[M-H-SO ₃ -C ₈ H ₈ O ₂ -CO ₂] ⁻	Urine
M29	Eriodictyol- <i>O</i> -glucuronide- <i>O</i> -sulfate	C ₂₁ H ₂₀ O ₁₅ S	9.9	543.0446	463.0877[M-H-SO ₃] ⁻ , 367.0121[M-H-GlcUA] ⁻ , 287.0553[M-H-SO ₃ -GlcUA] ⁻ , 254.9802, 175.0235[M-H-SO ₃ -EY] ⁻ , 151.0034[M-H-SO ₃ -GlcUA-C ₈ H ₈ O ₂] ⁻ , 135.0455[M-H-SO ₃ -GlcUA-C ₇ H ₄ O ₄] ⁻ , 113.0250[M-H-SO ₃ -EY-CO ₂ -H ₂ O] ⁻ , 107.0125[M-H-SO ₃ -GlcUA-C ₈ H ₈ O ₂ -CO ₂] ⁻ , 95.0149, 85.0310[M-H-SO ₃ -EY-CO ₂ -H ₂ O-CO] ⁻	Urine
M30	Hesperetin ^b	C ₁₆ H ₁₄ O ₆	13.8	301.0720	286.0501[M-H-CH ₃] ⁻ , 177.0177[M-H-C ₇ H ₈ O ₂] ⁻ , 151.0034[M-H-C ₉ H ₁₀ O ₂] ⁻ , 134.0372, 107.0132[M-H-C ₉ H ₁₀ O ₂ -CO ₂] ⁻ , 95.0889, 83.0146	Urine
M31	Hesperetin-5- <i>O</i> -glucuronide	C ₂₂ H ₂₂ O ₁₂	11.6	477.1034	301.0716[M-H-GlcUA] ⁻ , 286.0470[M-H-GlcUA-CH ₃] ⁻ , 177.0186[M-H-GlcUA-C ₇ H ₈ O ₂] ⁻ , 175.0236[M-H-HE] ⁻ , 151.0029[M-H-GlcUA-C ₉ H ₁₀ O ₂] ⁻ , 134.0365[M-H-GlcUA-C ₇ H ₄ O ₄ -CH ₃] ⁻ , 113.0243[M-H-HE-CO ₂ -H ₂ O] ⁻ , 99.0102, 85.0286[M-H-HE-CO ₂ -H ₂ O-CO] ⁻	Urine
M32	Hesperetin-7- <i>O</i> -glucuronide ^b	C ₂₂ H ₂₂ O ₁₂	11.8	477.1040	301.0719[M-H-GlcUA] ⁻ , 286.0477[M-H-GlcUA-CH ₃] ⁻ , 242.0552[M-H-GlcUA-OCH ₂ -HCO] ⁻ , 175.0240[M-H-HE] ⁻ , 151.0026[M-H-GlcUA-C ₉ H ₁₀ O ₂] ⁻ , 113.0244[M-H-HE-CO ₂ -H ₂ O] ⁻ , 95.0146, 85.0315[M-H-HE-CO ₂ -H ₂ O-CO] ⁻	Urine
M33	Hesperetin-3'- <i>O</i> -glucuronide ^b	C ₂₂ H ₂₂ O ₁₂	12.4	477.1041	360.9595, 301.0702[M-H-GlcUA] ⁻ , 286.0452[M-H-GlcUA-CH ₃] ⁻ , 151.0030[M-H-GlcUA-C ₉ H ₁₀ O ₂] ⁻ , 113.0248[M-H-HE-CO ₂ -H ₂ O] ⁻	Urine

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M34	Hesperetin- <i>O</i> -diglucuronide	C ₂₈ H ₃₀ O ₁₈	9.6	653.1362 (0.4)	477.1007[M-H-GlcUA] ⁻ , 301.0702[M-H-2GlcUA] ⁻ , 175.0221[M-H-HE-GlcUA] ⁻ , 151.0018[M-H-2GlcUA-C ₉ H ₁₀ O ₂] ⁻ , 113.0238[M-H-HE-GlcUA-CO ₂ -H ₂ O] ⁻ , 85.0315[M-H-HE-GlcUA-CO ₂ -H ₂ O-CO] ⁻	Urine
M35	Hesperetin-3'- <i>O</i> -sulfate	C ₁₆ H ₁₄ O ₉ S	11.9	381.0282 (-0.9)	301.0706[M-H-SO ₃] ⁻ , 286.0464[M-H-SO ₃ -CH ₃] ⁻ , 205.0829, 165.9884[M-H-SO ₃ -C ₈ H ₈ O ₂] ⁻ , 110.0009	Urine
M36	Hesperetin-7- <i>O</i> -sulfate ^b	C ₁₆ H ₁₄ O ₉ S	12.3	381.0279 (-1.7)	301.0716[M-H-SO ₃] ⁻ , 286.0478[M-H-SO ₃ -CH ₃] ⁻ , 177.0177[M-H-SO ₃ -C ₇ H ₈ O ₂] ⁻ , 151.0038[M-H-SO ₃ -C ₉ H ₁₀ O ₂] ⁻ , 134.0377[M-H-SO ₃ -C ₇ H ₄ O ₄ -CH ₃] ⁻ , 107.0136[M-H-SO ₃ -C ₉ H ₁₀ O ₂ -CO ₂] ⁻	Urine
M37	Hesperetin- <i>O</i> -glucuronide- <i>O</i> -sulfate	C ₂₂ H ₂₂ O ₁₅ S	9.4	557.0579 (-4.9)	477.1032[M-H-SO ₃] ⁻ , 383.1930, 381.0252[M-H-GlcUA] ⁻ , 301.0719[M-H-GlcUA-SO ₃] ⁻ , 254.9808, 175.0258[M-H-SO ₃ -HE] ⁻ , 151.0022[M-H-GlcUA-SO ₃ -C ₉ H ₁₀ O ₂] ⁻ , 113.0221[M-H-SO ₃ -HE-CO ₂ -H ₂ O] ⁻	Urine
M38	Hesperetin- <i>O</i> -glucuronide- <i>O</i> -sulfate	C ₂₂ H ₂₂ O ₁₅ S	10.3	557.0597 (-1.8)	477.1038[M-H-SO ₃] ⁻ , 381.0272[M-H-GlcUA] ⁻ , 301.0718[M-H-GlcUA-SO ₃] ⁻ , 254.9800, 175.0236[M-H-SO ₃ -HE] ⁻ , 151.0035[M-H-GlcUA-SO ₃ -C ₉ H ₁₀ O ₂] ⁻ , 113.0247[M-H-SO ₃ -HE-CO ₂ -H ₂ O] ⁻ , 85.0309[M-H-SO ₃ -HE-CO ₂ -H ₂ O-CO] ⁻	Urine
M39	Hesperetin- <i>O</i> -glucoside- <i>O</i> -sulfate	C ₂₂ H ₂₄ O ₁₄ S	9.4	543.0805 (-1.6)	463.1235[M-H-SO ₃] ⁻ , 383.1926, 301.0705[M-H-SO ₃ -Glc] ⁻ , 287.0521, 151.0010[M-H-SO ₃ -Glc-C ₉ H ₁₀ O ₂] ⁻ , 113.0248	Urine

^a The losses are: Rha= rhamnose moiety, Glc = glucose moiety, GlcUA = glucuronyl moiety, NE = naringenin, AE=apigenin, EY = eriodictyol, HE = hesperetin.

^b Confirmation in comparison with authentic standards.

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Table S4. UFLC-Q-TOF-MS/MS based identifications of phenolic catabolites in rat urine and feces samples collected 0-48 h after a single oral administration of naringin.

No.	Identified metabolites	Formula	RT (min)	[M-H] ⁻ (Error, ppm)	Fragment ions in negative mode ^a	Source
C1	Chromone derivatives					
	5,7-Dihydroxychromone ^b	C ₉ H ₆ O ₄	9.4	177.0206 (4.9)	133.0272[M-H-CO ₂] ⁻ , 109.0286, 91.0186, 77.0405	Urine
C2	Benzenetriol derivatives					
	Phloroglucinol ^b	C ₆ H ₆ O ₃	6.7	125.0255 (3.5)	81.0315[M-H-CO ₂] ⁻	Urine
C3	Phloroglucinol- <i>O</i> -sulfate	C ₆ H ₆ O ₆ S	6.7	204.9814 (0.8)	125.0235[M-H-SO ₃] ⁻ , 81.0360[M-H-SO ₃ -CO ₂] ⁻	Urine
C4	Phenylpropenoic acid derivatives					
	Feruloylglycine	C ₁₂ H ₁₃ NO ₅	9.6	250.0722 (0.2)	232.0602[M-H-H ₂ O] ⁻ , 206.0811[M-H-CO ₂] ⁻ , 188.0736[M-H-H ₂ O-CO ₂] ⁻ , 162.0913[M-H-CO ₂ -CH ₄ -CO] ⁻ , 132.0309[M-H-CO ₂ -C ₂ H ₄ NO-CH ₄] ⁻ , 121.0295, 88.0403	Urine
C5	3-(4'-Methoxyphenyl)-2-propenoic acid-3'- <i>O</i> -glucuronide	C ₁₆ H ₁₈ O ₁₀	8.3	369.0827 (0.1)	324.0246[M-H-COOH] ⁻ , 289.9186, 251.1105, 193.0496[M-H-GlcUA] ⁻ , 178.0256[M-H-GlcUA-CH ₃] ⁻ , 175.0233[M-H-3H4MPEA] ⁻ , 149.0590[M-H- GlcUA-CO ₂] ⁻ , 134.0360[M-H-GlcUA-CO ₂ -CH ₃] ⁻ , 113.0228[M-H- 3H4MPEA-CO ₂ -H ₂ O] ⁻ , 85.0293[M-H-3H4MPEA-CO ₂ -H ₂ O-CO] ⁻	Urine
C6	3-(4'-Methoxyphenyl)-2-propenoic acid-3'- <i>O</i> -sulfate	C ₁₀ H ₁₀ O ₇ S	8.8	273.0077 (0.9)	229.0146[M-H-CO ₂] ⁻ , 193.0496[M-H-SO ₃] ⁻ , 178.0260[M-H-SO ₃ -CH ₃] ⁻ , 149.0597[M-H-SO ₃ -CO ₂] ⁻ , 134.0364[M-H-SO ₃ -CO ₂ -CH ₃] ⁻ , 96.9602	Urine
C7	Caffeic acid-4'- <i>O</i> -sulfate	C ₉ H ₈ O ₇ S	5.2	258.9924 (2.3)	214.9990[M-H-CO ₂] ⁻ , 187.0061[M-H-CO ₂ -CO] ⁻ , 179.0322[M-H-SO ₃] ⁻ , 135.0429[M-H-SO ₃ -CO ₂] ⁻ , 107.0492[M-H-SO ₃ -CO ₂ -CO] ⁻ , 93.0352, 80.9649	Urine
C8	Caffeic acid-3'- <i>O</i> -sulfate	C ₉ H ₈ O ₇ S	5.7	258.9922 (1.7)	215.0004[M-H-CO ₂] ⁻ , 187.0068[M-H-CO ₂ -CO] ⁻ , 179.0330[M-H-SO ₃] ⁻ , 135.0446[M-H-SO ₃ -CO ₂] ⁻ , 107.0505[M-H-SO ₃ -CO ₂ -CO] ⁻ , 93.0353	Urine

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C9	Caffeic acid- <i>O</i> -glucuronide	C ₁₅ H ₁₆ O ₁₀	5.3	355.0665 (-1.5)	283.0792, 179.0340[M-H-GlcUA] ⁻ , 175.0272[M-H-CA] ⁻ , 113.0257[M-H-CA-CO ₂ -H ₂ O] ⁻ , 107.0467[M-H-GlcUA-CO ₂ -CO] ⁻ , 85.0315[M-H-CA-CO ₂ -H ₂ O-CO] ⁻	Urine
C10	3-(4'-Hydroxyphenyl)-2-propenoic acid	C ₉ H ₈ O ₃	10.9	163.0408 (4.2)	119.0494[M-H-CO ₂] ⁻ , 93.0356[M-H-CO ₂ -2CH] ⁻	Urine, Feces
C11	3-(3'-Hydroxyphenyl)-2-propenoic acid	C ₉ H ₈ O ₃	11.5	163.0410 (4.6)	119.0500[M-H-CO ₂] ⁻ , 93.0325[M-H-CO ₂ -2CH] ⁻ , 91.0572[M-H-CO ₂ -CO] ⁻	Urine
C12	3-(Phenyl)-2-propenoic acid-4'- <i>O</i> -sulfate	C ₉ H ₈ O ₆ S	8.6	242.9971 (0.9)	163.0401[M-H-SO ₃] ⁻ , 119.0509[M-H-SO ₃ -CO ₂] ⁻ , 96.9618, 91.0521[M-H-SO ₃ -CO ₂ -CO] ⁻	Urine
C13	3-(Phenyl)-2-propenoic acid-3'- <i>O</i> -sulfate	C ₉ H ₈ O ₆ S	9.4	242.9970 (0.6)	163.0391[M-H-SO ₃] ⁻ , 119.0498[M-H-SO ₃ -CO ₂] ⁻ , 91.0565[M-H-SO ₃ -CO ₂ -CO] ⁻	Urine
C14	3-(Phenyl)-2-propenoic acid-4'- <i>O</i> -glucuronide	C ₁₅ H ₁₆ O ₉	9.4	339.0724 (0.7)	175.0217[M-H-4HPEA] ⁻ , 163.0587[M-H-GlcUA] ⁻ , 119.0505[M-H-GlcUA-CO ₂] ⁻ , 113.0244[M-H-4HPEA-CO ₂ -H ₂ O] ⁻ , 85.0304[M-H-4HPEA-CO ₂ -H ₂ O-CO] ⁻	Urine
C15	3-(Phenyl)-2-propenoic acid-3'- <i>O</i> -glucuronide	C ₁₅ H ₁₆ O ₉	10.4	339.0718 (-0.9)	175.0237[M-H-3HPEA] ⁻ , 163.0390[M-H-GlcUA] ⁻ , 119.0503[M-H-GlcUA-CO ₂] ⁻ , 113.0247[M-H-3HPEA-CO ₂ -H ₂ O] ⁻ , 103.0062, 85.0305[M-H-3HPEA-CO ₂ -H ₂ O-CO] ⁻	Urine
	Phenylpropionic acid derivatives					
C16	3-(3'-Hydroxy-4'-methoxyphenyl)hydracrylic acid	C ₁₀ H ₁₂ O ₅	11.6	211.0613 (0.6)	193.0496[M-H-H ₂ O] ⁻ , 167.0699[M-H-CO ₂] ⁻ , 123.0809[M-H-CO ₂ -C ₂ H ₄ O] ⁻ , 95.0523[M-H-CO ₂ -C ₂ H ₄ O-CO] ⁻	Urine, Feces
C17	3-(3'-Hydroxy-4'-methoxyphenyl)propionic acid	C ₁₀ H ₁₂ O ₄	12.0	195.0667 (2.1)	160.8426, 151.0739[M-H-CO ₂] ⁻ , 123.0403[M-H-CO ₂ -CO] ⁻ , 107.0847[M-H-CO ₂ -CO-CH ₄] ⁻	Urine, Feces
C18	3-(4'-Methoxyphenyl)propionic acid-3'- <i>O</i> -sulfate	C ₁₀ H ₁₂ O ₇ S	8.2	275.0230 (-0.4)	195.0650[M-H-SO ₃] ⁻ , 177.0547[M-H-SO ₃ -H ₂ O] ⁻ , 151.0786[M-H-SO ₃ -CO ₂] ⁻ , 133.0646[M-H-SO ₃ -CO ₂ -H ₂ O] ⁻ , 123.0445[M-H-SO ₃ -CO ₂ -CO] ⁻ , 81.0360	Urine, Feces
C19	3-(4'-Methoxyphenyl)propionic	C ₁₆ H ₂₀ O ₁₀	10.6	371.0965	327.1336[M-H-CO ₂] ⁻ , 283.0813[M-H-2CO ₂] ⁻ , 241.9922, 195.0606[M-H-	Urine

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	acid-3'- <i>O</i> -glucuronide			(-5.0)	GlcUA] ⁻ , 175.0255[M-H-3H4MPPA] ⁻ , 151.0760[M-H-GlcUA-CO ₂] ⁻ , 113.0249[M-H-3H4MPPA-CO ₂ -H ₂ O] ⁻ , 96.9640, 85.0303[M-H-3H4MPPA-CO ₂ -H ₂ O-CO] ⁻	
C20	3-(3',4'-Dihydroxyphenyl)propionic acid	C ₉ H ₁₀ O ₄	7.9	181.0507 (0.3)	163.0384[M-H-H ₂ O] ⁻ , 135.0431[M-H-H ₂ O-CO] ⁻ , 119.0493[M-H-H ₂ O-CO ₂] ⁻ , 107.0482[M-H-H ₂ O-2CO] ⁻ , 93.0368	Urine, Feces
C21	3-(3'-Hydroxyphenyl)propionic acid-4'- <i>O</i> -sulfate	C ₉ H ₁₀ O ₇ S	7.0	261.0074 (-0.3)	217.0180[M-H-CO ₂] ⁻ , 181.0498[M-H-SO ₃] ⁻ , 137.0607[M-H-SO ₃ -CO ₂] ⁻ , 122.0372[M-H-SO ₃ -CO ₂ -CH ₃] ⁻ , 95.0508, 79.9577	Urine, Feces
C22	3-(4'-Hydroxyphenyl)propionic acid-3'- <i>O</i> -sulfate	C ₉ H ₁₀ O ₇ S	8.0	261.0077 (0.8)	181.0495[M-H-SO ₃] ⁻ , 137.0600[M-H-SO ₃ -CO ₂] ⁻ , 135.0446[M-H-SO ₃ -HCOOH] ⁻ , 121.0287[M-H-SO ₃ -CO ₂ -CH ₄] ⁻ , 109.0282[M-H-SO ₃ -CO ₂ -CO] ⁻ , 79.9578	Urine
C23	3-(3'-Hydroxyphenyl)propionic acid-4'- <i>O</i> -glucuronide	C ₁₅ H ₁₈ O ₁₀	6.0	357.0825 (-0.5)	181.0486[M-H-GlcUA] ⁻ , 175.0261[M-H-3H4HPPA] ⁻ , 137.0596[M-H-GlcUA-CO ₂] ⁻ , 113.0236[M-H-3H4HPPA-CO ₂ -H ₂ O] ⁻ , 85.0312[M-H-3H4HPPA-CO ₂ -H ₂ O-CO] ⁻	Urine, Feces
C24	3-(4'-Hydroxyphenyl)propionic acid-3'- <i>O</i> -glucuronide	C ₁₅ H ₁₈ O ₁₀	6.7	357.0825 (-0.7)	181.0491[M-H-GlcUA] ⁻ , 175.0258[M-H-3H4HPPA] ⁻ , 137.0587[M-H-GlcUA-CO ₂] ⁻ , 135.0461[M-H-GlcUA-HCOOH] ⁻ , 113.0238[M-H-3H4HPPA-CO ₂ -H ₂ O] ⁻ , 85.0317[M-H-3H4HPPA-CO ₂ -H ₂ O-CO] ⁻	Urine, Feces
C25	3-(4'-Hydroxyphenyl)propionic acid ^b	C ₉ H ₁₀ O ₃	10.2	165.0572 (4.2)	121.0634[M-H-CO ₂] ⁻ , 119.0510[M-H-HCOOH] ⁻ , 93.0358[M-H-CO ₂ -C ₂ H ₄] ⁻	Urine, Feces
C26	3-(3'-Hydroxyphenyl)propionic acid	C ₉ H ₁₀ O ₃	10.8	165.0573 (4.4)	121.0662[M-H-CO ₂] ⁻ , 119.0507[M-H-HCOOH] ⁻ , 106.0429[M-H-CO ₂ -CH ₃] ⁻ , 93.0356[M-H-CO ₂ -C ₂ H ₄] ⁻	Urine, Feces
C27	3-(Phenyl)propionic acid-4'- <i>O</i> -sulfate	C ₉ H ₁₀ O ₆ S	8.3	245.0139 (5.4)	165.0550[M-H-SO ₃] ⁻ , 121.0659[M-H-SO ₃ -CO ₂] ⁻ , 119.0504[M-H-SO ₃ -HCOOH] ⁻ , 93.0360[M-H-SO ₃ -CO ₂ -C ₂ H ₄] ⁻ , 79.9596	Urine
C28	3-(Phenyl)propionic acid-3'- <i>O</i> -sulfate	C ₉ H ₁₀ O ₆ S	8.6	245.0137 (4.7)	165.0548[M-H-SO ₃] ⁻ , 121.0655[M-H-SO ₃ -CO ₂] ⁻ , 119.0503[M-H-SO ₃ -HCOOH] ⁻ , 106.0428[M-H-SO ₃ -CO ₂ -CH ₃] ⁻ , 93.0350[M-H-SO ₃ -CO ₂ -C ₂ H ₄] ⁻ , 79.9591	Urine
C29	3-(Phenyl)propionic acid-4'- <i>O</i> -	C ₁₅ H ₁₈ O ₉	8.2	341.0886	297.1001[M-H-CO ₂] ⁻ , 279.0890[M-H-CO ₂ -H ₂ O] ⁻ , 175.0227[M-H-4HPPA] ⁻ ,	Urine

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	glucuronide			(2.2)	165.0544[M-H-GlcUA] ⁻ , 113.0240[M-H-4HPPA-CO ₂ -H ₂ O] ⁻ , 80.9670	
C30	3-(Phenyl)propionic acid-3'- <i>O</i> -glucuronide	C ₁₅ H ₁₈ O ₉	8.9	341.0875 (-0.9)	297.0979[M-H-CO ₂] ⁻ , 165.0553[M-H-GlcUA] ⁻ , 121.0661[M-H-GlcUA-CO ₂] ⁻ , 113.0249[M-H-3HPPA-CO ₂ -H ₂ O] ⁻ , 80.9662	Urine
	Phenylacetic acid derivatives					
C31	3',4'-Dihydroxyphenylacetic acid	C ₈ H ₈ O ₄	5.1	167.0357 (4.2)	121.0258[M-H-HCOOH] ⁻ , 93.0359[M-H-HCOOH-CO] ⁻	Urine
C32/C33	4'-Hydroxyphenylacetic acid or 3'-Hydroxyphenylacetic acid	C ₈ H ₈ O ₃	9.0	151.0408 (5.0)	107.0507[M-H-CO ₂] ⁻ , 79.9613	Urine, Feces
C34	Phenylacetic acid-4'- <i>O</i> -sulfate	C ₈ H ₈ O ₆ S	6.0	230.9971 (0.9)	151.0399[M-H-SO ₃] ⁻ , 121.0484, 107.0497[M-H-SO ₃ -CO ₂] ⁻	Urine
C35	Phenylacetic acid-3'- <i>O</i> -sulfate	C ₈ H ₈ O ₆ S	7.2	230.9970 (0.6)	187.0068[M-H-CO ₂] ⁻ , 151.0406[M-H-SO ₃] ⁻ , 107.0507[M-H-SO ₃ -CO ₂] ⁻ , 95.9522, 79.9597	Urine, Feces
C36	Phenylacetic acid-4'- <i>O</i> -glucuronide	C ₁₄ H ₁₆ O ₉	6.3	327.0719 (-0.7)	283.0802[M-H-CO ₂] ⁻ , 175.0207[M-H-4HPAA] ⁻ , 151.0384[M-H-GlcUA] ⁻ , 113.0228[M-H-4HPAA-CO ₂ -H ₂ O] ⁻ , 107.0504[M-H-GlcUA-CO ₂] ⁻ , 99.0078, 87.0091	Urine
C37	Phenylacetic acid-3'- <i>O</i> -glucuronide	C ₁₄ H ₁₆ O ₉	7.0	327.0722 (0.2)	283.0808[M-H-CO ₂] ⁻ , 193.0332, 175.0230[M-H-3HPAA] ⁻ , 151.0405[M-H-GlcUA] ⁻ , 124.0129, 113.0241[M-H-3HPAA-CO ₂ -H ₂ O] ⁻ , 107.0500[M-H-GlcUA-CO ₂] ⁻	Urine
	Benzoic acid derivatives					
C38	3-Hydroxybenzoic acid	C ₇ H ₆ O ₃	6.8	137.0256 (4.9)	93.0339[M-H-CO ₂] ⁻	Urine
C39	4-Hydroxybenzoic acid ^b	C ₇ H ₆ O ₃	9.0	137.0257 (5.9)	93.0352[M-H-CO ₂] ⁻	Urine, Feces
C40	Benzoic acid-4- <i>O</i> -sulfate	C ₇ H ₆ O ₆ S	6.4	216.9823 (4.7)	137.0244[M-H-SO ₃] ⁻ , 93.0356[M-H-SO ₃ -CO ₂] ⁻	Urine
C41	Benzoic acid-3- <i>O</i> -sulfate	C ₇ H ₆ O ₆ S	6.9	216.9820	137.0241[M-H-SO ₃] ⁻ , 93.0358[M-H-SO ₃ -CO ₂] ⁻	Urine

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				(4.9)			
C42	Benzoic acid-4- <i>O</i> -glucuronide	C ₁₃ H ₁₄ O ₉	6.1	313.0565	193.0348[M-H-C ₇ H ₄ O ₂] ⁻ , 175.0229[M-H-4HBA] ⁻ , 137.0241[M-H-GlcUA] ⁻ , (0.1) 113.0222[M-H-4HBA-CO ₂ -H ₂ O] ⁻ , 85.0296[M-H-4HBA-CO ₂ -H ₂ O-CO] ⁻	Urine	
C43	Benzoic acid-3- <i>O</i> -glucuronide	C ₁₃ H ₁₄ O ₉	6.8	313.0566	193.0343[M-H-C ₇ H ₄ O ₂] ⁻ , 175.0228[M-H-3HBA] ⁻ , 137.0241[M-H-GlcUA] ⁻ , (0.4) 113.0246[M-H-4HBA-CO ₂ -H ₂ O] ⁻ , 93.0381[M-H-GlcUA-CO ₂] ⁻	Urine	
	Benzoylglycine derivatives						
C44	Hippuric acid ^b	C ₉ H ₉ NO ₃	8.9	178.0522	134.0610[M-H-CO ₂] ⁻ , 102.0354, 77.0422 (6.8)	Urine, Feces	
C45/C46	4'-Hydroxyhippuric acid or 3'- Hydroxyhippuric acid	C ₉ H ₉ NO ₄	7.0	194.0464	150.0550[M-H-CO ₂] ⁻ , 132.0427[M-H-CO ₂ -H ₂ O] ⁻ , 100.0045, 93.0357 (2.8)	Urine	

^a The losses are: GlcUA = glucuronyl moiety, 3H4MPEA=3-(3'-hydroxy-4'-methoxyphenyl)-2-propenoic acid, CA=caffeic acid, 4HPEA=3-(4'-hydroxyphenyl)-2-propenoic acid, 3HPEA=3-(3'-hydroxyphenyl)-2-propenoic acid, 3H4MPPA=3-(3'-hydroxy-4'-methoxyphenyl)propionic acid, 3H4HPPA=3-(3',4'-Dihydroxyphenyl)propionic acid, 4HPPA=3-(4'-Hydroxyphenyl)propionic acid, 3HPPA=3-(3'-Hydroxyphenyl)propionic acid, 4HBA=4-hydroxybenzoic acid, 3HBA=3-hydroxybenzoic acid.

^b Confirmation in comparison with authentic standards.

Supplementary Materials

Table S5. The volumes (mL) of urine collected from 12 aged rats during each time period.

Time (h)	Rat 1	Rat 2	Rat 3	Rat 4	Rat 5	Rat 6	Rat 7	Rat 8	Rat 9	Rat 10	Rat 11	Rat 12
0-4	4.2	5.0	4.2	3.9	2.8	3.2	5.2	3.3	4.4	4.7	6.2	3.0
4-8	2.6	2.1	2.4	1.5	2.5	0.0	0.0	6.4	1.8	0.0	8.9	6.5
8-12	2.3	1.1	3.1	2.2	3.1	3.6	0.0	0.0	2.3	0.0	2.2	8.4
12-24	9.4	8.8	25.5	12.6	14.0	10.9	21.8	6.0	3.3	13.0	6.5	37.5
24-36	3.9	6.0	7.4	4.4	2.8	4.0	5.6	6.4	2.9	0.0	9.5	8.4
36-48	10.5	5.8	13.8	8.0	10.4	9.7	10.6	12.4	6.6	5.9	7.5	23.8

Table S6. The weight (mg) of feces collected from 12 aged rats during each time period.

Time (h)	Rat 1	Rat 2	Rat 3	Rat 4	Rat 5	Rat 6	Rat 7	Rat 8	Rat 9	Rat 10	Rat 11	Rat 12
0-4	685.8	0	0	0	0	0	0	1044.7	0	0	0	0
4-8	0	0	0	377.2	0	0	0	0	0	0	0	0
8-12	0	0	0	0	0	0	0	0	0	0	0	0
12-24	0	0	0	55.9	0	529.2	0	0	1088.1	0	275.1	0
24-36	0	612.7	0	0	0	0	0	1000.3	0	0	208.6	182.0
36-48	739.4	0	0	161.5	527.0	113.8	1073.8	0	0	0	1023.7	0

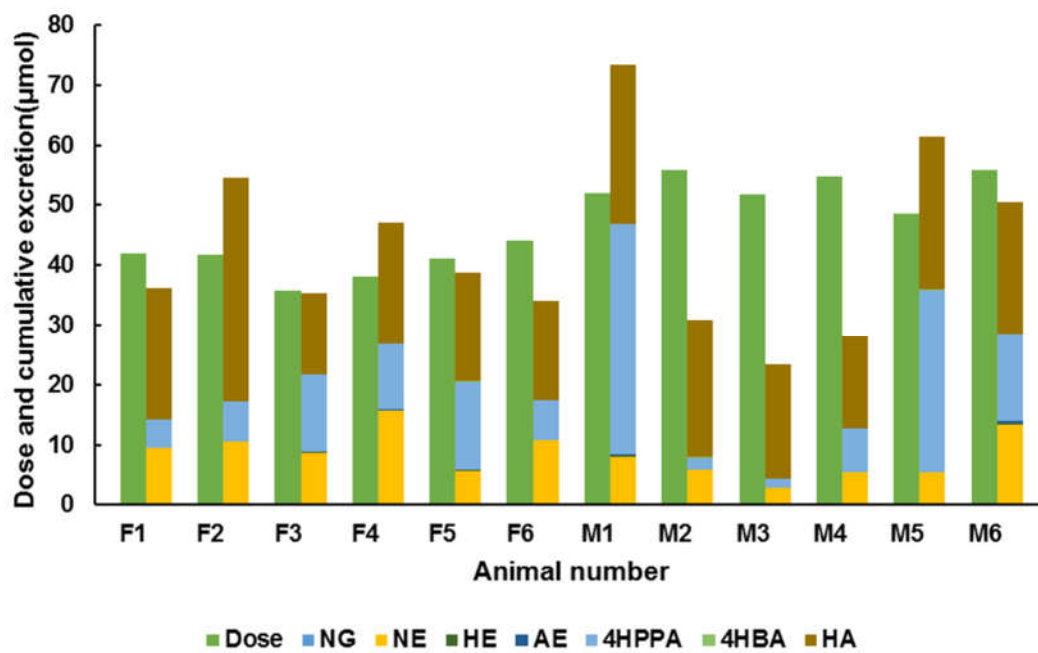


Fig. S1. Dose and cumulative excretion of naringin (NG) and its main metabolites (naringenin (NE), hesperetin (HE), apigenin (AE), hippuric acid (HA), 4-hydroxybenzoic acid (4HBA), and 3-(4'-hydroxyphenyl)propionic acid (4HPPA)) in twelve aged rats.