Combinatorial Metabolism Notably Affects Human Systemic Exposure to Ginsenosides from Orally Administered Extract of *Panax notoginseng* Roots (Sanqi)

Zheyi Hu, Junling Yang, Chen Cheng, Yuhong Huang, Feifei Du, Fengqing Wang, Wei Niu, Fang Xu, Rongrong Jiang, Xiumei Gao, Chuan Li

Drug Metabolism and Disposition

Supplemental Table 1

In vitro metabolism of compound-K, 20(*S*)-protopanaxadiol, and 20(*S*)-protopanaxatriol using human liver microsomes, rat liver microsomes or rat colon microsomes

Compound	*In vitro* metabolism $t_{1/2}$ (min) [cofactor]	Precursor/human metabolite information: Precursor or metabolite (change in mass, possible metabolic reaction)	Relative abundance (%)	t_R (min)	Parent ion** (*m/z*)	Product ion (*m/z*)
Compound-K	Human liver microsomes	Compound-K (0)	100	15.95	623	407, 425, 443
	>120 [1]/[2]/[3]*	**M1** (+16, epoxidation)	5	14.40	639	125, 143, 191, 405, 423, 441
	Rat liver microsomes	**M2** (+16, epoxidation)	10	14.51	639	125, 143, 191, 405, 423, 441
	>120 [1]/[2]/[3]	**M30** (+16, oxidation)	7	14.74	639	125, 143, 191, 405, 423, 441
	Rat colon microsomes					
	>120 [1]/[2]/[3]					
20(*S*)-Proto-panaxadiol	Human liver microsomes	Protopanaxadiol (0)	100	17.74	467	407, 425
	6 [1]/>120 [2]/4 [3]	**M16** (+34, alkenes to dihydrodiol)	2	13.95	495	125, 143, 191, 405, 423, 441, 459, 477
	Rat liver microsomes	**M17** (+32, oxidation)	24	14.30	493	125, 143, 191, 403, 421, 439, 457, 475
	20 [1]/>120 [2]/20 [3]	**M18** (+34, alkenes to dihydrodiol)	1	14.70	495	125, 143, 191, 405, 423, 441, 459, 477
	Rat colon microsomes	**M19** (+32, oxidation)	22	15.35	493	123, 141, 159, 191, 403, 421, 439, 457, 475
	>120 [1]/[2]/[3]	**M20** (+16, epoxidation)	69	15.51	477	125, 143, 191, 405, 423, 441, 459
		M21 (+16, epoxidation)	184	15.78	477	125, 143, 191, 405, 423, 441, 459
		M22 (+16, epoxidation)	24	16.22	477	125, 143, 191, 405, 423, 441, 459
		M34 (+46, oxidation/dehydrogenation)	8	12.70	507	125, 143, 417, 435, 453, 471, 489

		M35 (+48, oxidation)	2	13.34	509	159, 401, 419, 437, 455, 473, 491
		M36 (+192, oxidation/glucuronidation)	0.2	14.63	653	125, 143, 191, 405, 423, 441, 599, 617, 635
		M37 (+192, oxidation/glucuronidation)	0.2	14.74	653	125, 143, 191, 405, 423, 441, 599, 617, 635
		M38 (+192, oxidation/glucuronidation)	0.05	15.15	653	125, 143, 191, 405, 423, 441, 599, 617, 635
20(*S*)-Proto-	Human liver microsomes	Protopanaxatriol (0)	100	14.14	477	405, 423, 441, 459
panaxatriol	4 [1]/>120 [2]/5 [3]	**M3** (+34, alkenes to dihydrodiol)	5	9.36	511	125, 143, 189, 207, 403, 421, 439, 457, 475, 493
	Rat liver microsomes	**M4** (+32, oxidation)	130	9.45	509	141, 159, 189, 207, 401, 419, 437, 455, 473, 491
	4 [1]/>120 [2]/7 [3]	**M5** (+32, oxidation)	157	10.00	509	141, 159, 189, 207, 401, 419, 437, 455, 473, 491
	Rat colon microsomes	**M6** (+34, alkenes to dihydrodiol)	8	10.26	511	125, 143, 189, 207, 403, 421, 439, 457, 475, 493
	>120 [1]/[2]/[3]	**M7** (+30, oxidation/dehydrogenation)	40	10.45	507	141, 159, 417, 435, 453, 471, 489
		M8 (+32, oxidation)	848	10.97	509	141, 159, 189, 207, 401, 419, 437, 455, 473, 491
		M9 (+30, oxidation/dehydrogenation)	10	11.35	507	141, 159, 417, 435, 453, 471, 489
		M10 (+16, epoxidation)	158	11.76	493	125, 143, 189, 207, 403, 421, 439, 457, 475
		M11 (+32, oxidation)	233	12.11	509	125, 143, 187, 205, 401, 419, 437, 455, 473, 491
		M12 (+16, epoxidation)	2381	12.21	493	125, 143, 189, 207, 403, 421, 439, 457, 475
		M13 (+30, oxidation/dehydrogenation)	30	12.25	507	125, 143, 417, 435, 453, 471, 489
		M14 (+14, oxidation/dehydrogenation)	167	12.43	491	125, 143, 419, 437, 455, 473
		M15 (+14, oxidation/dehydrogenation)	211	13.07	491	125, 143, 419, 437, 455, 473
		M23 (+208, oxidation/glucuronidation)	0.2	8.22	685	141, 159, 189, 207, 419, 437, 455, 473, 509, 667
		M24 (+208, oxidation/glucuronidation)	0.2	9.10	685	141, 159, 189, 207, 419, 437, 455, 473, 509, 667
		M25 (+192, oxidation/glucuronidation)	1	9.16	669	125, 143, 189, 207, 403, 421, 439, 457, 651
		M26 (+208, oxidation/glucuronidation)	1	10.36	685	125, 143, 187, 205, 419, 437, 455, 473, 509, 667
		M27 (+192, oxidation/glucuronidation)	4	10.36	669	125, 143, 189, 207, 403, 421, 439, 457, 651
		M28 (+192, oxidation/glucuronidation)	0.3	11.40	669	125, 143, 189, 207, 403, 421, 439, 457, 651
		M29 (+176, glucuronidation)	5	11.90	653	477
		M31 (+208, oxidation/glucuronidation)	0.1	8.59	685	141, 159, 189, 207, 419, 437, 455, 473, 509, 667

		M32 (+208, oxidation/glucuronidation)	0.1	9.72	685	125, 143, 187, 205, 419, 437, 455, 473, 509, 667
		M33 (+32, oxidation)	174	11.73	509	125, 143, 187, 205, 401, 419, 437, 455, 473, 491

Human liver microsomes, rat liver microsomes, and rat colon microsomes showed in vitro metabolism $t_{1/2}$ values of 5, 4, and >120 min, respectively, for midazolam hydroxylation (the cofactor, NADPH) or 9, 14, and 16 min, respectively, for chrysin glucuronidation (the cofactor, UDPGA).

*[1], NADPH; [2], UDPGA; [3], NADPH + UDPGA.

**All the compounds were measured as protonated molecules, except for 20(*S*)-protopanaxadiol measured as lithiated adduct ion.