

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

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### Drug Metabolism and Disposition

### Supplemental Table 3

Human plasma pharmacokinetics and urinary excretion data of ginsenosides and their major metabolites after a single p.o. dose of Sanqi-extract at 90 ml/subject

Compound*	Sex	$C_{\max}$ (nM)	$T_{\max}$ (h)	$T_L$ (h)	$AUC_{0-t}$ (nM·h)	MRT (h)	$Cum.A_{e-0-72h}$ (nmol)	$CL_R$ (l/h)
<i>Ppd-type ginsenosides and the sapogenin</i>								
Ginsenoside Ra <sub>3</sub> (P/U-g)	Male	0.65 ± 0.16	20.1 ± 16.4	1.63 ± 1.03	19.4 ± 3.1	46.1 ± 8.4	1.76 ± 0.19	0.089 ± 0.020
	Female	0.61 ± 0.23	14.0 ± 6.9	1.00 ± 0.58	16.7 ± 8.0	47.8 ± 20.9	1.27 ± 0.59	0.090 ± 0.048
Ginsenoside Rb <sub>1</sub> (P/U-g)	Male	8.35 ± 2.10	8.50 ± 4.93	0.50 ± 0	336 ± 109	49.2 ± 6.9	19.4 ± 5.2	0.066 ± 0.017
	Female	6.17 ± 2.36	5.75 ± 5.17	0.50 ± 0	117 ± 61	53.2 ± 7.5	13.1 ± 5.5	0.070 ± 0.025
Ginsenoside Rd (P/U-g)	Male	1.81 ± 0.46	11.8 ± 2.9	0.75 ± 0.50	59.2 ± 26.3	41.5 ± 15.2	1.57 ± 0.39	0.031 ± 0.014
	Female	2.33 ± 1.18	10.8 ± 3.4	0.50 ± 0	61.8 ± 40.6	31.1 ± 7.5	1.55 ± 0.41	0.032 ± 0.018
Ginsenoside F <sub>2</sub> (P/U-g)	Male	0.78 ± 0.18	14.3 ± 1.5	10.1 ± 3.8	12.4 ± 5.2	32.4 ± 5.5	0.179 ± 0.127	0.013 ± 0.009
	Female	0.83 ± 0.28	12.8 ± 1.5	4.50 ± 0	12.1 ± 3.7	21.6 ± 2.3	0.224 ± 0.116	0.017 ± 0.008
Compound-K (P/U-m)	Male	90.1 ± 14.6	15.0 ± 0	0.50 ± 0	1514 ± 469	24.0 ± 3.0	29.6 ± 8.3	0.020 ± 0.007
	Female	152 ± 67	11.8 ± 2.9	0.50 ± 0	2183 ± 839	18.5 ± 4.3	39.2 ± 12.9	0.018 ± 0.002
20(S)-Protopanaxadiol (P-m)	Female	5.77	27.0	19.5	161	88.3	–	–
20(S)-Protopanaxadiol (P-m)	Female	8.18 ± 5.28	21.0 ± 10.4	13.5 ± 11.0	181 ± 34	27.0 ± 7.7	–	–
<i>Ppt-type ginsenosides and the sapogenin</i>								
Notoginsenoside R <sub>1</sub> (P/U-g)	Male	0.33 ± 0.14	6.25 ± 4.91	0.50 ± 0	1.02 ± 0.55	6.67 ± 3.52	23.8 ± 7.4	22.2 ± 16.5
	Female	0.30 ± 0.10	1.00 ± 0.58	0.75 ± 0.50	0.97 ± 0.86	11.4 ± 9.6	20.2 ± 4.3	30.0 ± 19.6
Ginsenoside Rg <sub>1</sub> (P/U-g)	Male	1.83 ± 0.86	2.88 ± 3.45	0.50 ± 0	11.1 ± 5.2	9.35 ± 2.94	158 ± 67	10.7 ± 3.7
	Female	1.99 ± 0.58	0.75 ± 0.50	0.50 ± 0	10.3 ± 2.9	6.86 ± 2.02	130 ± 31	11.2 ± 1.9
Ginsenoside F <sub>1</sub> (P/U-g)	Male	1.50 ± 1.06	16.5 ± 5.2	7.13 ± 4.80	18.3 ± 6.3	31.6 ± 14.0	9.27 ± 3.23	0.449 ± 0.139
	Female	1.57 ± 0.74	16.4 ± 9.6	1.13 ± 1.25	12.3 ± 6.0	13.0 ± 6.1	10.2 ± 6.0	0.661 ± 0.257
20(S)-Protopanaxatiol (P-m)	Male	57.3 ± 51.4	33.5 ± 11.7	3.13 ± 1.89	1142 ± 899	38.8 ± 6.2	–	–
	Female	57.0 ± 23.5	26.0 ± 11.0	2.13 ± 1.97	1064 ± 481	32.0 ± 15.9	–	–
<i>Metabolites of 20(S)-protopanaxadiol</i>								
<b>M16</b> (P/U-m)	Male	4.92 ± 5.16	25.3 ± 9.5	10.0 ± 2.3	106 ± 75	32.0 ± 4.8	2.35 ± 1.37	0.023 ± 0.012
	Female	5.65 ± 2.27	25.3 ± 9.5	7.25 ± 3.57	135 ± 92	33.2 ± 8.3	2.38 ± 0.77	0.020 ± 0.007

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<b>M17</b> (P-m)	Male	13.5 ± 10.0	32.5 ± 6.8	11.0 ± 2.0	336 ± 230	51.6 ± 14.9	–	–
	Female	18.1 ± 8.8	35.0 ± 14.3	6.25 ± 2.02	477 ± 262	36.6 ± 2.6	–	–
<b>M19</b> (P-m)	Male	13.1 ± 8.9	37.0 ± 13.9	12.8 ± 1.5	382 ± 255	48.1 ± 10.8	–	–
	Female	21.8 ± 8.0	35.0 ± 14.3	9.00 ± 2.00	593 ± 283	34.6 ± 3.4	–	–
<b>M20</b> (P-m)	Male	7.05 ± 4.48	27.5 ± 7.0	13.5 ± 1.7	184 ± 125	39.1 ± 5.3	–	–
	Female	11.9 ± 6.0	30.5 ± 18.6	9.00 ± 2.00	260 ± 134	27.9 ± 5.1	–	–
<b>M21</b> (P-m)	Male	28.8 ± 19.7	32.0 ± 16.0	11.0 ± 2.0	846 ± 519	48.7 ± 12.2	–	–
	Female	48.2 ± 19.1	30.5 ± 18.6	6.30 ± 2.00	1273 ± 593	34.0 ± 7.1	–	–
<b>M22</b> (P-m)	Male	5.18 ± 3.38	29.0 ± 6.6	17.3 ± 4.5	144 ± 95	47.0 ± 16.5	–	–
	Female	10.8 ± 4.8	24.8 ± 7.1	12.0 ± 8.0	230 ± 102	30.2 ± 7.8	–	–
<b>M34</b> (U-m)	Male	–	–	–	–	–	32.8 ± 20.8	1.73 ± 1.10
	Female	–	–	–	–	–	59.1 ± 34.4	3.11 ± 1.81
<b>M35</b> (U-m)	Male	–	–	–	–	–	75.7 ± 45.8	3.98 ± 2.41
	Female	–	–	–	–	–	120 ± 89	6.29 ± 4.70
<i>Metabolites of 20(S)-protopanaxatriol</i>								
<b>M4</b> (P/U-m)	Male	27.8 ± 21.5	33.5 ± 11.7	18.8 ± 6.2	599 ± 466	54.4 ± 24.8	39.2 ± 34.4	0.058 ± 0.014
	Female	33.1 ± 8.6	26.8 ± 9.7	9.00 ± 2.00	701 ± 311	37.8 ± 21.3	53.1 ± 44.2	0.067 ± 0.036
<b>M5</b> (P/U-m)	Male	31.0 ± 27.2	33.5 ± 11.7	18.8 ± 6.2	635 ± 561	38.4 ± 6.4	319 ± 278	0.504 ± 0.093
	Female	36.9 ± 10.8	26.8 ± 9.7	10.8 ± 3.4	716 ± 335	33.9 ± 15.3	292 ± 232	0.368 ± 0.166
<b>M6</b> (P/U-m)	Male	10.1 ± 6.9	29.0 ± 6.6	18.8 ± 6.2	213 ± 142	40.9 ± 11.1	275 ± 180	1.31 ± 0.23
	Female	8.31 ± 4.05	23.3 ± 6.2	12.8 ± 1.5	181 ± 116	41.2 ± 29.3	260 ± 226	1.21 ± 0.55
<b>M7</b> (P/U-m)	Male	10.4 ± 8.5	31.0 ± 8.1	19.5 ± 5.2	227 ± 197	38.9 ± 4.3	107 ± 82	0.493 ± 0.082
	Female	11.1 ± 2.8	29.3 ± 13.9	14.0 ± 6.9	250 ± 113	31.7 ± 4.5	140 ± 92	0.537 ± 0.212
<b>M8</b> (P/U-m)	Male	300 ± 231	33.5 ± 11.7	2.88 ± 3.45	5969 ± 4618	39.6 ± 5.5	813 ± 596	0.137 ± 0.013
	Female	340 ± 103	26.8 ± 9.7	1.75 ± 1.89	6704 ± 2460	34.1 ± 16.8	968 ± 637	0.134 ± 0.055
<b>M10</b> (P/U-m)	Male	59.0 ± 62.2	33.5 ± 11.7	11.8 ± 2.9	1169 ± 1043	38.3 ± 5.4	24.3 ± 18.1	0.026 ± 0.012
	Female	41.4 ± 17.0	26.8 ± 9.7	9.00 ± 2.00	921 ± 535	37.6 ± 18.8	20.2 ± 17.3	0.021 ± 0.012
<b>M11</b> (P/U-m)	Male	102 ± 84	33.5 ± 11.7	15.8 ± 5.7	2327 ± 1861	46.0 ± 8.8	124 ± 104	0.051 ± 0.013
	Female	112 ± 34	29.3 ± 13.9	8.13 ± 3.07	2603 ± 1190	42.4 ± 21.2	149 ± 112	0.053 ± 0.019
<b>M12</b> (P/U-m)	Male	741 ± 586	33.5 ± 11.7	0.50 ± 0	15127 ± 11927	39.6 ± 6.1	131 ± 95	0.009 ± 0.001
	Female	809 ± 282	26.8 ± 9.7	0.50 ± 0	16533 ± 7600	33.4 ± 13.7	180 ± 110	0.010 ± 0.003
<b>M13</b> (P/U-m)	Male	19.9 ± 15.4	34.5 ± 7.0	19.5 ± 5.2	518 ± 396	42.3 ± 6.2	166 ± 132	0.308 ± 0.019
	Female	23.8 ± 9.1	29.3 ± 13.9	9.75 ± 3.5	578 ± 264	34.1 ± 5.8	188 ± 133	0.306 ± 0.091
<b>M14</b> (P/U-m)	Male	18.7 ± 15.4	34.5 ± 7.0	15.8 ± 5.7	452 ± 342	50.2 ± 14.7	22.5 ± 13.1	0.062 ± 0.032
	Female	20.0 ± 7.4	31.5 ± 11.4	11.8 ± 2.9	511 ± 205	50.5 ± 23.3	28.0 ± 12.5	0.056 ± 0.016
<b>M15</b> (P/U-m)	Male	7.68 ± 6.05	32.5 ± 6.8	6.25 ± 6.71	195 ± 138	44.2 ± 7.6	12.9 ± 8.7	0.067 ± 0.010
	Female	8.30 ± 3.00	29.3 ± 13.9	4.38 ± 5.42	213 ± 77	41.0 ± 16.4	15.8 ± 6.4	0.072 ± 0.008
<b>M23</b> (U-m)	Male	–	–	–	–	–	–	8.97 ± 1.38
	Female	–	–	–	–	–	89.3 ± 94.0	12.4 ± 10.5

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<b>M24</b> (U-m)	Male	–	–	–	–	–	311 ± 237	14.7 ± 2.3
	Female	–	–	–	–	–	369 ± 307	11.0 ± 4.9
<b>M25</b> (U-m)	Male	–	–	–	–	–	117 ± 97	8.69 ± 1.77
	Female	–	–	–	–	–	131 ± 120	12.5 ± 4.8
<b>M27</b> (U-m)	Male	–	–	–	–	–	284 ± 213	36.4 ± 29.9
	Female	–	–	–	–	–	326 ± 344	15.2 ± 8.4
<b>M29</b> (U-m)	Male	–	–	–	–	–	163 ± 137	6.69 ± 0.93
	Female	–	–	–	–	–	200 ± 162	6.30 ± 3.17

$C_{\max}$ : maximum plasma concentration;  $T_{\max}$ : time taken to achieve the maximum concentration;  $T_L$ : lag time for occurrence in plasma;  $AUC_{0 \rightarrow t}$ : area under concentration-time curve up to the last measured time point; MRT: mean residence time;  $Cum.A_{e0 \rightarrow 72h}$ : cumulative amount excreted in the urine during sampling period;  $CL_R$ : renal clearance.

\*P/U-g, plasma/urinary ginsenoside; P/U-m, plasma/urinary metabolite; P-m, plasma metabolite; U-m, urinary metabolite.