Intravenous formulation of *Panax notoginseng* root extract: human pharmacokinetics of ginsenosides and potential for perpetrating drug interactions

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Supplementary Table S1. Ginsenosides present in XueShuanTong

ID	Compound	Liquid chromatography/mass spectrometry data			Molecular mass (Da)	Molecular formula	Compound dose level (μmol/day) (RSD)
		t_R (min)	$[M-H]^-$ (*m/z*)	Fragmentation profile (*m/z*)			
Ppd-type ginsenosides							
1	Ginsenoside Rb_1	24.03	1107.5948	945.5441 $[M-H-Glc]^-$ 783.4908 $[M-H-2Glc]^-$ 621.4377 $[M-H-3Glc]^-$ 459.3820 $[M-H-4Glc]^-$	1108.6029	$C_{54}H_{92}O_{23}$	112.74 ± 7.89 (7.0%)
2	Ginsenoside Rd	25.64	945.5411	783.4921 $[M-H-Glc]^-$ 621.4380 $[M-H-2Glc]^-$ 459.3849 $[M-H-3Glc]^-$	946.5501	$C_{48}H_{82}O_{18}$	4.25 ± 0.79 (18.6%)
3	Notoginsenoside Fa	23.55	1239.6377	1107.5973 $[M-H-Xyl]^-$ 945.5430 $[M-H-Xyl-Glc]^-$ 783.4887 $[M-H-Xyl-2Glc]^-$ 621.4361 $[M-H-Xyl-3Glc]^-$	1240.6452	$C_{59}H_{100}O_{27}$	3.16 ± 0.23 (7.3%)
4	Ginsenoside Ra_3	23.82	1239.6357	1107.5972 $[M-H-Xyl]^-$ 945.5421 $[M-H-Xyl-Glc]^-$ 783.4893 $[M-H-Xyl-2Glc]^-$ 621.4333 $[M-H-Xyl-3Glc]^-$	1240.6452	$C_{59}H_{100}O_{27}$	3.22 ± 0.25 (7.9%)
5	Notoginsenoside R_4	23.02	1239.6378	1107.6008 $[M-H-Xyl]^-$ 945.5449 $[M-H-Xyl-Glc]^-$ 783.4935 $[M-H-Xyl-2Glc]^-$ 621.4390 $[M-H-Xyl-3Glc]^-$	1240.6452	$C_{59}H_{100}O_{27}$	1.56 ± 0.20 (13.1%)
6	Ginsenoside F_2	28.08	783.4886	621.4373 $[M-H-Glc]^-$ 459.3830 $[M-H-2Glc]^-$	784.4973	$C_{42}H_{72}O_{13}$	1.33 ± 0.49 (36.7%)
7	Notoginsenoside D/T isomer-1	22.52	1371.6759	1239.6340 $[M-H-Xyl]^-$ 1107.5901 $[M-H-2Xyl]^-$ 1077.5787 $[M-H-Xyl-Glc]^-$ 945.5456 $[M-H-2Xyl-Glc]^-$ 783.4897 $[M-H-2Xyl-2Glc]^-$	1372.6875	$C_{64}H_{108}O_{31}$	0.46 ± 0.04 (8.5%)
8	Ginsenoside Rb_3	24.86	1077.5859	945.5410 $[M-H-Xyl]^-$ 783.4888 $[M-H-Xyl-Glc]^-$ 621.4354 $[M-H-Xyl-2Glc]^-$ 459.3837 $[M-H-Xyl-3Glc]^-$	1078.5924	$C_{53}H_{90}O_{22}$	0.51 ± 0.07 (14.5%)
9	Notoginsenoside K	26.48	945.5416	783.4841 $[M-H-Glc]^-$ 621.4367 $[M-H-2Glc]^-$ 459.3826 $[M-H-3Glc]^-$	946.5503	$C_{48}H_{82}O_{18}$	0.24 ± 0.07 (28.9%)
10	Notoginsenoside D/T isomer-2	23.33	1371.6797	1239.6438 $[M-H-Xyl]^-$ 1107.5981 $[M-H-2Xyl]^-$ 1077.5912 $[M-H-Xyl-Glc]^-$ 945.5427 $[M-H-2Xyl-Glc]^-$ 783.4919 $[M-H-2Xyl-2Glc]^-$ 621.4391 $[M-H-2Xyl-3Glc]^-$ 459.3825 $[M-H-2Xyl-4Glc]^-$	1372.6875	$C_{64}H_{108}O_{31}$	0.33 ± 0.03 (8.1%)
11	Quinquenoside V isomer-1	22.93	1269.6479	1107.5946 $[M-H-Glc]^-$ 945.5421 $[M-H-2Glc]^-$ 783.4882 $[M-H-3Glc]^-$ 621.4387 $[M-H-4Glc]^-$ 459.3850 $[M-H-5Glc]^-$	1270.6559	$C_{60}H_{102}O_{28}$	0.38 ± 0.06 (16.6%)
12	Quinquenoside V isomer-2	23.45	1269.6501	1107.5957 $[M-H-Glc]^-$ 945.5429 $[M-H-2Glc]^-$ 783.4895 $[M-H-3Glc]^-$ 621.4370 $[M-H-4Glc]^-$ 459.3845 $[M-H-5Glc]^-$	1270.6559	$C_{60}H_{102}O_{28}$	0.16 ± 0.01 (8.1%)
13	Ginsenoside Rg_3	28.20	783.4897	621.4298 $[M-H-Glc]^-$ 459.3831 $[M-H-2Glc]^-$	784.4973	$C_{42}H_{72}O_{13}$	0.13 ± 0.02 (14.1%)
14	Ginsenoside Ra_1	24.25	1209.6285	1077.5844 $[M-H-Xyl]^-$ 945.5416 $[M-H-Xyl-Ara(p)]^-$ 915.5331 $[M-H-Xyl-Glc]^-$ 783.4883 $[M-H-Xyl-Ara(p)-Glc]^-$ 621.4365 $[M-H-Xyl-Ara(p)-2Glc]^-$ 459.3831 $[M-H-Xyl-Ara(p)-3Glc]^-$	1210.6346	$C_{58}H_{98}O_{26}$	0.07 ± 0.01 (13.5%)
Ppt-type ginsenosides							
31	Ginsenoside Rg1	18.56	799.4852	637.4321 $[M-H-Glc]^-$ 475.3781 $[M-H-2Glc]^-$	800.4922	$C_{42}H_{72}O_{14}$	260.30 ± 17.84 (6.9%)
32	Notoginsenoside R_1	17.77	931.5284	799.4848 $[M-H-Xyl]^-$ 769.4742 $[M-H-Glc]^-$ 637.4324 $[M-H-Xyl-Glc]^-$	932.5345	$C_{47}H_{80}O_{18}$	42.61 ± 1.88 (4.4%)

				475.3786 $[M-H-Xyl-2Glc]^-$			
33	Ginsenoside Re	18.46	945.5432	799.4844 $[M-H-Rha]^-$ 783.4907 $[M-H-Glc]^-$ 637.4319 $[M-H-Rha-Glc]^-$ 475.3784 $[M-H-Rha-2Glc]^-$	946.5501	$C_{48}H_{82}O_{18}$	27.91 ± 2.84 (10.2%)
34	Ginsenoside Rh_1	22.23	637.4316	475.3785 $[M-H-Glc]^-$	638.4394	$C_{36}H_{62}O_9$	2.52 ± 0.78 (30.9%)
35	20-Gluco-ginsenoside Rf	17.54	961.5363	799.4852 $[M-H-Glc]^-$ 637.4310 $[M-H-2Glc]^-$ 475.3774 $[M-H-3Glc]^-$	962.5450	$C_{48}H_{82}O_{19}$	3.41 ± 0.26 (7.6%)
36	Ginsenoside Rg_2	22.09	783.4889	637.4315 $[M-H-Rha]^-$ 475.3782 $[M-H-Rha-Glc]^-$	784.4973	$C_{42}H_{72}O_{13}$	2.42 ± 0.34 (14.2%)
37	Notoginsenoside $M/N/R_3/R_6$ isomer-3	16.75	961.5341	799.4866 $[M-H-Glc]^-$ 637.4319 $[M-H-2Glc]^-$ 475.3783 $[M-H-3Glc]^-$	962.5450	$C_{48}H_{82}O_{19}$	1.55 ± 0.20 (12.6%)
38	20-Gluco-ginsenoside Rf isomer	17.10	961.5366	799.4865 $[M-H-Glc]^-$ 637.4318 $[M-H-2Glc]^-$ 475.3774 $[M-H-3Glc]^-$	962.5450	$C_{48}H_{82}O_{19}$	0.86 ± 0.06 (6.7%)
39	Notoginsenoside $M/N/R_3/R_6$ isomer-1	21.23	961.5366	799.4856 $[M-H-Glc]^-$ 637.4326 $[M-H-2Glc]^-$ 475.3789 $[M-H-3Glc]^-$	962.5450	$C_{48}H_{82}O_{19}$	0.67 ± 0.03 (4.9%)
40	Ginsenoside Rf	21.33	799.4866	637.4308 $[M-H-Glc]^-$ 475.3783 $[M-H-2Glc]^-$	800.4922	$C_{42}H_{72}O_{14}$	0.65 ± 0.04 (5.6%)
41	Notoginsenoside $M/N/R_3/R_6$ isomer-4	18.08	961.5349	799.4819 $[M-H-Glc]^-$ 637.4303 $[M-H-2Glc]^-$ 475.3775 $[M-H-3Glc]^-$	962.5450	$C_{48}H_{82}O_{19}$	0.76 ± 0.04 (4.9%)
42	Notoginsenoside $M/N/R_3/R_6$	16.97	961.5342	799.4843 $[M-H-Glc]^-$ 637.4318 $[M-H-2Glc]^-$ 475.3785 $[M-H-3Glc]^-$	962.5450	$C_{48}H_{82}O_{19}$	0.63 ± 0.06 (10.3%)
43	Yesanchinoside E	16.86	1107.6007	945.5452 $[M-H-Glc]^-$ 783.4927 $[M-H-2Glc]^-$ 637.4318 $[M-H-Rha-2Glc]^-$ 475.3777 $[M-H-Rha-3Glc]^-$	1108.6031	$C_{54}H_{92}O_{23}$	0.47 ± 0.02 (4.2%)
44	Notoginsenoside $M/N/R_3/R_6$ isomer-2	18.26	961.5377	799.4825 $[M-H-Glc]^-$ 637.4310 $[M-H-2Glc]^-$ 475.3763 $[M-H-3Glc]^-$	962.5450	$C_{48}H_{82}O_{19}$	0.42 ± 0.03 (6.2%)
45	Notoginsenoside Rw_1 isomer-2	21.59	901.5161	769.4763 $[M-H-Xyl]^-$ 637.4333 $[M-H-2Xyl]^-$ 475.3784 $[M-H-2Xyl-Glc]^-$	902.5240	$C_{46}H_{78}O_{17}$	0.36 ± 0.03 (9.5%)
46	Ginsenoside F_1	23.16	637.4316	475.3762 $[M-H-Glc]^-$	638.4394	$C_{36}H_{62}O_9$	0.25 ± 0.05 (18.0%)
47	Notoginsenoside Rw_1 isomer-1	19.35	901.5175	769.4630 $[M-H-Xyl]^-$ 637.4266 $[M-H-2Xyl]^-$ 475.3740 $[M-H-2Xyl-Glc]^-$	902.5240	$C_{46}H_{78}O_{17}$	0.16 ± 0.02 (12.4%)
48	Notoginsenoside R_2 isomer/Ginsenoside F_3 isomer	19.84	769.4751	637.4315 $[M-H-Xyl]^-$/ $[M-H-Ara(p)]^-$ 475.3786 $[M-H-Xyl-Glc]^-$/ $[M-H-Ara(p)-Glc]^-$	770.4818	$C_{41}H_{70}O_{13}$	0.07 ± 0.03 (45.3%)
Ginsenosides of other types							
51	Notoginsenoside G isomer-1	19.37	959.5239	797.4719 $[M-H-Glc]^-$ 635.4163 $[M-H-2Glc]^-$	960.5295	$C_{48}H_{80}O_{19}$	0.55 ± 0.01 (2.6%)
52	Koryoginsenoside R_2/ Notoginsenoside A isomer-3	20.40	1123.5948	961.5411 $[M-H-Glc]^-$ 637.4330 $[M-H-3Glc]^-$ 475.3785 $[M-H-4Glc]^-$	1124.5980	$C_{54}H_{92}O_{24}$	0.56 ± 0.03 (6.0%)
53	Notoginsenoside B/ Quinquenoside IV isomer-1	17.61	1121.5775	959.5234 $[M-H-Glc]^-$	1122.5823	$C_{54}H_{90}O_{24}$	0.37 ± 0.08 (20.4%)
54	Yesanchinoside H isomer-1	16.10	1093.5778	961.5405 $[M-H-Xyl]^-$ 931.5297 $[M-H-Glc]^-$ 799.4866 $[M-H-Glc-Xyl]^-$ 769.4646 $[M-H-2Glc]^-$ 637.4330 $[M-H-2Glc-Xyl]^-$ 475.3788 $[M-H-3Glc-Xyl]^-$	1094.5874	$C_{53}H_{90}O_{23}$	0.40 ± 0.06 (14.6%)
55	Koryoginsenoside Rg_2/ Notoginsenoside A isomer-4	20.95	1123.5928	961.5388 $[M-H-Glc]^-$ 799.4866 $[M-H-2Glc]^-$ 637.4308 $[M-H-3Glc]^-$ 475.3791 $[M-H-4Glc]^-$	1124.598	$C_{54}H_{92}O_{24}$	0.30 ± 0.07 (24.1%)
56	5,6-Didehydroginsenoside Rb_1	23.52	1105.5815	943.5246 $[M-H-Glc]^-$	1106.5873	$C_{54}H_{90}O_{23}$	0.49 ± 0.04 (8.3%)
57	Notoginsenoside I	23.65	1091.6012	929.5482 $[M-H-Glc]^-$ 767.4954 $[M-H-2Glc]^-$ 605.4413 $[M-H-3Glc]^-$	1092.6082	$C_{54}H_{92}O_{22}$	0.49 ± 0.07 (14.3%)
58	Koryoginsenoside Rg_2/ Notoginsenoside A isomer-1	19.30	1123.5925	961.5386 $[M-H-Glc]^-$ 799.4844 $[M-H-2Glc]^-$ 637.4326 $[M-H-3Glc]^-$	1124.598	$C_{54}H_{92}O_{24}$	0.32 ± 0.03 (7.9%)

				475.3626 $[M-H-4Glc]^-$			
59	Quinquenoside L_{16}	19.10	1141.6051	979.5528 $[M-H-Glc]^-$ 799.4851 $[M-H-H_2O-2Glc]^-$ 637.4312 $[M-H-H_2O-3Glc]^-$ 475.3780 $[M-H-H_2O-4Glc]^-$	1142.6084	$C_{54}H_{94}O_{25}$	0.29 ± 0.05 (15.8%)
60	Quinquenoside L_{16} isomer	18.26	1141.6042	961.5417 $[M-H-H_2O-Glc]^-$ 799.4868 $[M-H-H_2O-2Glc]^-$ 637.4333 $[M-H-H_2O-3Glc]^-$ 475.3786 $[M-H-H_2O-4Glc]^-$	1142.6084	$C_{54}H_{94}O_{25}$	0.31 ± 0.05 (16.1%)
61	Notoginsenoside E isomer-2	19.79	979.5460	961.5380 $[M-H-H_2O]^-$ 799.4850 $[M-H-H_2O-Glc]^-$ 655.4412 $[M-H-2Glc]^-$ 493.3905 $[M-H-3Glc]^-$	980.5556	$C_{48}H_{84}O_{20}$	0.19 ± 0.03 (15.5%)
62	Notoginsenoside B/ Quinquenoside IV isomer-2	20.08	1121.5787	959.5152 $[M-H-Glc]^-$ 797.4713 $[M-H-2Glc]^-$	1122.5823	$C_{54}H_{90}O_{24}$	0.21 ± 0.02 (7.3%)
63	Yesanchinoside H isomer-2	16.42	1093.5789	961.5409 $[M-H-Xyl]^-$ 931.5429 $[M-H-Glc]^-$ 799.4819 $[M-H-Glc-Xyl]^-$ 769.4747 $[M-H-2Glc]^-$ 637.4329 $[M-H-2Glc-Xyl]^-$ 475.3787 $[M-H-3Glc-Xyl]^-$	1094.5874	$C_{53}H_{90}O_{23}$	0.19 ± 0.02 (11.5%)
64	Notoginsenoside E isomer-1	18.90	979.5485	799.4822 $[M-H-H_2O-Glc]^-$ 637.4326 $[M-H-H_2O-2Glc]^-$ 475.3773 $[M-H-H_2O-3Glc]^-$	980.5556	$C_{48}H_{84}O_{20}$	0.11 ± 0.02 (19.6%)
65	Yesanchinoside H isomer-4	17.56	1093.5780	961.5394 $[M-H-Xyl]^-$ 799.4847 $[M-H-Glc-Xyl]^-$ 637.4310 $[M-H-2Glc-Xyl]^-$ 475.3773 $[M-H-3Glc-Xyl]^-$	1094.5874	$C_{53}H_{90}O_{23}$	0.23 ± 0.06 (27.8%)
66	Yesanchinoside H isomer-3	17.02	1093.5767	961.5400 $[M-H-Xyl]^-$ 799.4834 $[M-H-Glc-Xyl]^-$ 637.4322 $[M-H-2Glc-Xyl]^-$ 475.3786 $[M-H-3Glc-Xyl]^-$	1094.5874	$C_{53}H_{90}O_{23}$	0.11 ± 0.02 (15.5%)
67	Koryoginsenoside Rg_2/ Notoginsenoside A isomer-2	19.68	1123.5952	961.5386 $[M-H-Glc]^-$ 799.4740 $[M-H-2Glc]^-$ 637.4316 $[M-H-3Glc]^-$ 475.3773 $[M-H-4Glc]^-$	1124.5980	$C_{54}H_{92}O_{24}$	0.09 ± 0.02 (26.2%)
68	Notoginsenoside G isomer-2	21.83	959.5220	797.4769$[M-H-Glc]^-$ 635.4115 $[M-H-2Glc]^-$	960.5295	$C_{48}H_{80}O_{19}$	0.07 ± 0.02 (27.2%)

The details of detection, characterization, and quantification of ginsenosides in XueShuanTong samples are described in 'MATERIALS AND METHODS' section ('Analysis of XueShuanTong samples for ginsenosides'). The dose level data represent the mean ± standard deviation for samples of five lots of XueShuanTong. Glc, glucopyranosyl; Ara(*p*), arabinopyranosyl; Rha, rhamnopyranosyl; Xyl, xylopyranosyl.

Supplementary Table S2. Ginsenosides, unchanged and metabolized, detected in plasma and urine samples after intravenously dosing XueShuanTong in the first human study

ID	Compound	Liquid chromatography/mass spectrometry data			Molecular mass (Da)	Molecular formula	Occurrence
		t_R (min)	$[M-H]^-$ $[M+Li]^{+\,\Delta}$ (*m/z*)	Fragmentation profile (*m/z*)			
Ppd-type ginsenosides							
1	Ginsenoside Rb_1	24.38	1107.5950	945.5410 $[M-H-Glc]^-$ 783.4878 $[M-H-2Glc]^-$ 621.4364 $[M-H-3Glc]^-$ 459.3835 $[M-H-4Glc]^-$	1108.6029	$C_{54}H_{92}O_{23}$	Plasma, urine
2	Ginsenoside Rd	25.93	945.5420	783.4822 $[M-H-Glc]^-$ 621.4364 $[M-H-2Glc]^-$ 459.3839$[M-H-3Glc]^-$	946.5501	$C_{48}H_{82}O_{18}$	Plasma, urine
3	Notoginsenoside Fa	23.88	1239.6350	1107.5928 $[M-H-Xyl]^-$ 945.5412 $[M-H-Xyl-Glc]^-$ 783.4875 $[M-H-Xyl-2Glc]^-$ 621.4438 $[M-H-Xyl-3Glc]^-$	1240.6452	$C_{59}H_{100}O_{27}$	Plasma, urine
4	Ginsenoside Ra_3	24.15	1239.6368	1107.5931 $[M-H-Xyl]^-$ 945.5334 $[M-H-Xyl-Glc]^-$ 783.4847 $[M-H-Xyl-2Glc]^-$ 621.4455 $[M-H-Xyl-3Glc]^-$	1240.6452	$C_{59}H_{100}O_{27}$	Plasma, urine
5	Notoginsenoside R_4	23.35	1239.6343	1107.5996 $[M-H-Xyl]^-$ 945.5383 $[M-H-Xyl-Glc]^-$ 783.4833 $[M-H-Xyl-2Glc]^-$ 621.4552 $[M-H-Xyl-3Glc]^-$	1240.6452	$C_{59}H_{100}O_{27}$	Plasma, urine
Ppt-type ginsenosides							
31	Ginsenoside Rg_1	18.84	799.4838	637.4308 $[M-H-Glc]^-$ 475.3768 $[M-H-2Glc]^-$	800.4922	$C_{42}H_{72}O_{14}$	Plasma, urine
32	Notoginsenoside R_1	18.04	931.5286	799.5023 $[M-H-Xyl]^-$ 769.4864 $[M-H-Glc]^-$ 637.4287 $[M-H-Xyl-Glc]^-$ 475.3754 $[M-H-Xyl-2Glc]^-$	932.5345	$C_{47}H_{80}O_{18}$	Plasma, urine
33	Ginsenoside Re	18.73	945.5438	799.4750 $[M-H-Rha]^-$ 783.4831 $M-H-Glc]^-$ 637.4395 $[M-H-Rha-Glc]^-$ 475.3739 $[M-H-Rha-2Glc]^-$	946.5501	$C_{48}H_{82}O_{18}$	Plasma, urine
34	Ginsenoside Rh_1	23.80	645^{Δ}	465 $[M+Li-H_2O-Glc]^+$	638.4394	$C_{36}H_{62}O_9$	Plasma, urine
35	20-Gluco-ginsenoside Rf	18.21	969^{Δ}	349 $[M+Li-PPD-Glc]^+$	962.5450	$C_{48}H_{82}O_{19}$	Plasma only
36	Ginsenoside Rg_2	22.74	791^{Δ}	465 $[M+Li-H_2O-Glc-Rha]^+$	784.4973	$C_{42}H_{72}O_{13}$	Plasma, urine
Metabolites of ppt-type ginsenosides							
PPT	20(*S*)-protopanaxatriol	26.42	483^{Δ}	465 $[M+Li-H_2O]^+$	476.3866	$C_{30}H_{52}O_4$	Plasma only
Metabolites of 20(S)-protopanaxatriol							
M_3	Oxidized metabolite	17.82	517^{Δ}	499 $[M+Li-H_2O]^+$	510.3920	$C_{30}H_{54}O_6$	Urine only
M_4	Oxidized metabolite	17.99	515^{Δ}	399 $[M+Li-116]^+$	508.3764	$C_{30}H_{52}O_6$	Plasma, urine
M_5	Oxidized metabolite	18.90	515^{Δ}	399 $[M+Li-116]^+$	508.3764	$C_{30}H_{52}O_6$	Urine only
M_6	Oxidized metabolite	19.39	517^{Δ}	499 $[M+Li-H_2O]^+$	510.3920	$C_{30}H_{54}O_6$	Plasma, urine
M_7	Oxidized/dehydrogenated metabolite	19.42	513^{Δ}	495 $[M+Li-H_2O]^+$	506.3607	$C_{30}H_{50}O_6$	Urine only
M_8	Oxidized metabolite	20.46	515^{Δ}	399 $[M+Li-116]^+$	508.3764	$C_{30}H_{52}O_6$	Plasma, urine
M_{11}	Oxidized metabolite	20.63	515^{Δ}	497 $[M+Li-H_2O]^+$	508.3764	$C_{30}H_{52}O_6$	Plasma, urine
M_{12}	Oxidized metabolite	22.68	499^{Δ}	481 $[M+Li-H_2O]^+$	492.3815	$C_{30}H_{52}O_5$	Plasma, urine
M_{13}	Oxidized/dehydrogenated metabolite	22.46	513^{Δ}	495 $[M+Li-H_2O]^+$	506.3607	$C_{30}H_{50}O_6$	Plasma, urine
M_{14}	Oxidized/dehydrogenated metabolite	23.02	497^{Δ}	479 $[M+Li-H_2O]^+$	490.3658	$C_{30}H_{50}O_5$	Plasma, urine

The details of human study and bioanalytical assay are described in 'MATERIALS AND METHODS' section ('Human studies' and 'Analysis of human samples for unchanged and metabolized ginsenosides', respectively). Due to assay sensitivity, some minor ginsenosides and the metabolites were detected and characterized using an AB Sciex API 4000 Q Trap mass spectrometer, interfaced via a Turbo V ion source with an Agilent 1290 Infinity II liquid chromatograph and the mobile phase contained 0.025 mmol/L lithium acetate. The data represent mean ± standard deviation. Glc, glucopyranosyl; Rha, rhamnopyranosyl; Xyl, xylopyranosyl.

Supplementary Table S3. Pharmacokinetics of midazolam and its metabolite 1'-hydroxymidazolam in human subjects of human study 2

Day	C_{max} (nmol/L)	$AUC_{0\text{-}8h}$ (nmol/L·h)	$AUC_{0\text{-}\infty}$ (nmol/L·h)	$t_{1/2}$ (h)
Midazolam				
Day 1	168.9 ± 79.9	298.0 ± 121.3	314.5 ± 129.0	1.7 ± 0.4
Day 4	254.2 ± 155.2	316.7 ± 115.3	336.9 ± 127.1	2.0 ± 0.6
Day 18	223.6 ± 58.3	359.5 ± 98.8	381.8 ± 108.8	2.1 ± 0.2
1'-hydroxymidazolam				
Day 1	63.8 ± 29.1	91.0 ± 39.2	97.0 ± 37.9	1.3 ± 0.4
Day 4	72.5 ± 28.7	81.6 ± 26.9	86.7 ± 27.4	1.3 ± 0.7
Day 18	62.1 ± 31.8	79.2 ± 31.8	86.1 ± 32.9	1.6 ± 0.8

The details of human study are described in 'MATERIALS AND METHODS' section ('Human studies'). On day 1, the subjects (m17–m24) received an oral dose of midazolam tablet at 7.5 mg. After 72-h washout period, they received a 2.5-h infusion of XueShuanTong daily for 15 days (from day 4 to day 18) at 500 mg per day. On days 4 and 18, the subjects also received an oral dose of midazolam tablet at 7.5 mg (just after terminating infusion of XueShuanTong on the day). The data represent mean ± standard deviation. C_{max}, maximum plasma concentration; $AUC_{0\text{-}8h}$, area under the plasma concentration-time curve from 0 to 8 h; $AUC_{0\text{-}\infty}$, area under the plasma concentration-time curve from 0 to infinity; $t_{1/2}$, terminal half-life.

Supplementary Table S4. In vitro inhibition of human P450 enzymes by ginsenosides

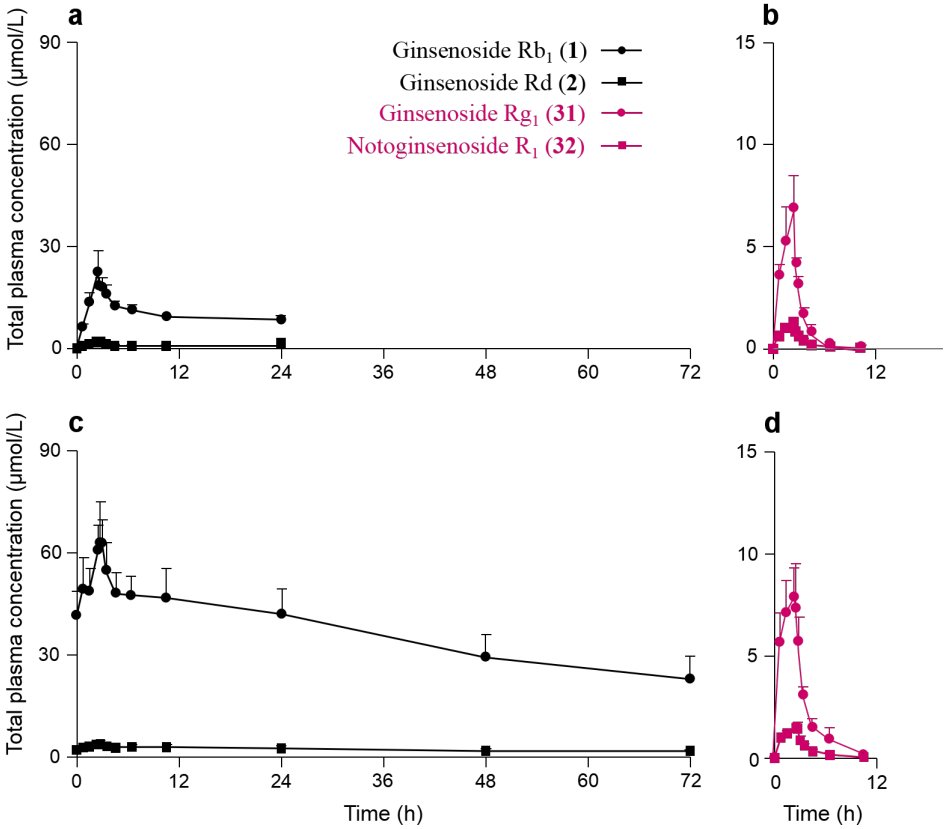
P450	IC_{50} (μmol/L)					
	Positive control	Ginsenoside Rb_1 (**1**)	Ginsenoside Rd (**2**)	Ginsenoside Rg_1 (**31**)	Notoginsenoside R_1 (**32**)	XueShuanTong (**XST**)
CYP3A	0.07	> 100	52.78	> 100	> 100	> 100
CYP1A2	6.96	> 100	> 100	> 100	> 100	> 100
CYP2A6	0.21	> 100	> 100	> 100	> 100	> 100
CYP2B6	3.69	> 100	> 100	> 100	> 100	> 100
CYP2D6	0.08	> 100	81.07	> 100	> 100	> 100
CYP2C8	0.26	> 100	96.20	> 100	> 100	> 100
CYP2C9	0.25	> 100	> 100	> 100	> 100	> 100
CYP2C19	5.75	> 100	56.21	> 100	> 100	> 100

The details of in vitro CYP3A inhibition study are described in 'MATERIALS AND METHODS' section ('In vitro assessment of CYP3A inhibition by XueShuanTong ginsenosides'). Inhibition of other human cytochrome P450 enzymes was assessed using human liver microsomes, the final concentrations of which were 0.1, 0.1, 0.2, 0.05, 0.05, 0.2, and 0.1 mg protein/mL for CYP1A2-, CYP2A6-, CYP2B6-, CYP2C8-, CYP2C9-, CYP2C19-, and CYP2D6-mediated metabolic reactions, respectively. Phenacetin, coumarin, bupropion, amodiaquine, diclofenac, (*S*)-mephenytoin, and dextromethorphan were used as probe substrates for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6, respectively; formation of acetaminophen, 7-hydroxycoumarin, hydroxybupropion, *N*-desmethylamodiaquine, 4'-hydroxydiclofenac, (*S*)-mephenytoin 4'-hydroxylation, and dextrorphan was measured individually by liquid chromatography/mass spectrometry-based assays for phenotyping of these P450 enzymes, respectively. Furafylline, tranylcypromine, quercetin, sulfaphenazole, and quinidine were used as positive inhibitors (positive controls) for CYP1A2, CYP2A6\2B6\2C19, CYP2C8, CYP2C9, and CYP2D6, respectively. Incubation times for CYP1A2-, CYP2A6-, CYP2B6-, CYP2C8-, CYP2C9-, CYP2C19-, and CYP2D6-mediated metabolic reactions were 20, 20, 20, 20, 10, 30, and 20 min, respectively.

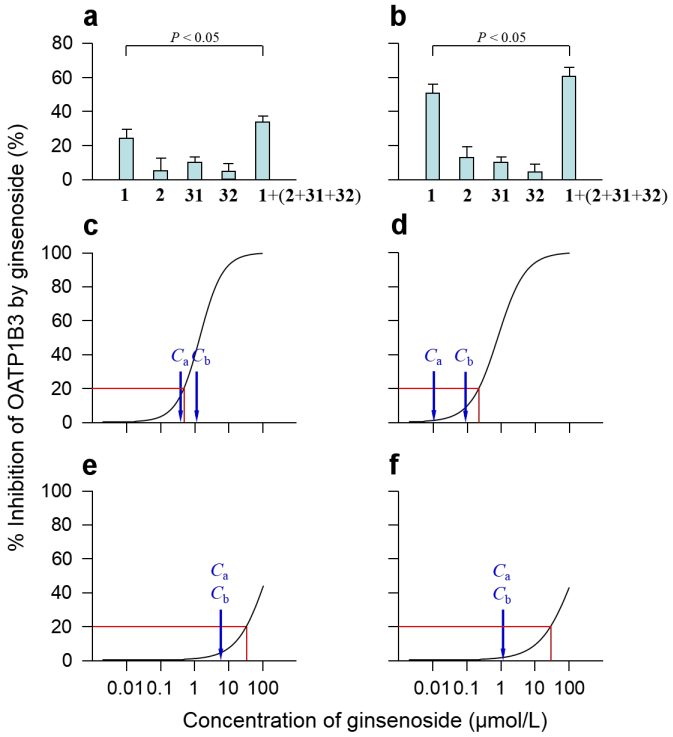
Supplementary Table S5. Pharmacokinetics of ginsenosides in rats after a single 15-min intravenous infusion of XueShuanTong

Compound (ID)	C_{max} (μmol/L)	$AUC_{0-\infty}$ (μmol/L·h)	$t_{1/2}$ (h)	$CL_{tot,p}$ (mL/h/kg)	V_{SS} (mL/kg)
Ginsenoside Rb_1 (**1**)	220.3 ± 25.0	2479 ± 272	17.1 ± 2.3	4.5 ± 0.5	106 ± 9
Ginsenoside Rd (**2**)	6.6 ± 0.3	172.7 ± 17.7	—	1.6 ± 1.0	109 ± 50
Ginsenoside Rg_1 (**31**)	101.7 ± 7.3	36 ± 6	1.3 ± 0.2	703.8 ± 111.0	203 ± 12
Notoginsenoside R_1 (**32**)	15.0 ± 2.8	7 ± 1	0.5 ± 0.1	657.0 ± 109.6	266 ± 13

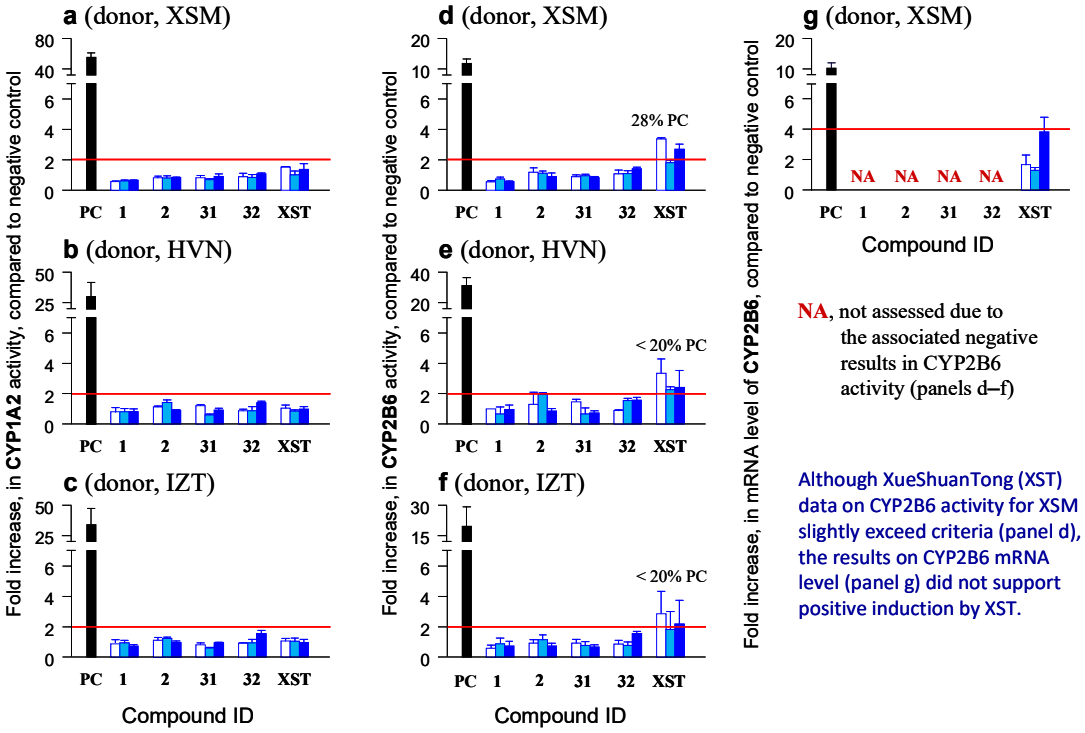
All animal care and use complied with the Guidance for Ethical Treatment of Laboratory Animals (The Ministry of Science and Technology of China, 2006, at www.most.gov.cn/fggw/zfwj/zfwj2006). Rat studies were implemented according to protocols that were reviewed and approved by the Institutional Animal Care and Use Committee at Shanghai Institute of Materia Medica (Shanghai, China). Male Sprague-Dawley rats were obtained from SIPPR-BK Laboratory Animal Co. Ltd. (Shanghai, China), housed at 20–24°C and relative humidity of 30%–70% with a 12-h light/dark cycle, and maintained under specific-pathogen-free conditions. Rats were provided commercial rat chow and access to filtered tap water ad libitum and were acclimated to the facilities and environment for one week before use. All rats received in-house femoral-vein-cannulation for infusion of XueShuanTong and femoral-artery-cannulation for blood sampling. After surgery, rats were housed singly and allowed to regain their preoperative body weights before the studies. To assess the systemic exposure to ginsenosides, six rats received a 15-min intravenous infusion of XueShuanTong at 50 mg/kg; the dose was translated from the label human dose of XueShuanTong (500 mg/day) by using a body surface area normalization method. Serial blood samples [around 150 μL; before and 5, 10, 15 (just before terminating the infusion), 20, 30, 45 min, and 1.25, 2.25, 4.25, 6.25, 8.25, 10.25, 24, 48, and 72 h after starting the infusion] were collected in heparinized tubes and then centrifuged to yield plasma fractions. The plasma samples were aliquoted and then stored at −70°C pending analysis. All used rats were euthanatized with CO_2 gas. The data represent mean ± standard deviation. C_{max}, maximum plasma concentration; $AUC_{0-\infty}$, area under the plasma concentration-time curve from 0 to infinity; $t_{1/2}$, terminal half-life; $CL_{tot,p}$, total plasma clearance; V_{SS}, apparent volume of distribution at steady state. AUC of ginsenoside Rd in this table was AUC_{0-72h}, rather than $AUC_{0-\infty}$; this is because there were continuous increases in plasma concentration from 10.25 to 48 h after intravenously dosing XueShuanTong in most rats. Due to this reason, it was difficult to estimate apparent $t_{1/2}$ of ginsenoside Rd. The unusual change in plasma concentration of ginsenoside Rd after dosing XueShuanTong most likely resulted from biotransformation of concurrent ginsenoside Rb_1 into ginsenoside Rd by rat hepatic glucosidase. More details pending publication elsewhere.



Supplementary Fig. S1 Mean total plasma concentrations of ginsenosides Rb_1 (**1**), Rd (**2**), and Rg_1 (**31**) and notoginsenoside R_1 (**32**) over time after dosing XueShuanTong at 500 mg/day on days 4 (**a**, **b**) and 18 (**c**, **d**) in human subjects (m17–m24; human study 2). The repeated dosing of XueShuanTong was started on day 4 and ended on day 18. Blood samples were collected for only 24 h after dosing on day 4.



Supplementary Fig. S2 Comparative % inhibition of OATP1B3 by ginsenoside Rb_1 (**1**) alone and in the presence of ginsenosides Rd (**2**) and Rg_1 (**31**) and notoginsenoside R_1 (**32**). In panel a, concentrations (C_a) of ginsenosides Rb_1 (**1**), Rd (**2**), and Rg_1 (**31**), and notoginsenoside R_1 (**32**) were the compounds' unbound C_{max} after the single dose of XueShuanTong, i.e., 0.39, 0.01, 6.07, and 1.18 μmol/L, respectively, and the compounds' concentrations in '**1** + (**2** + **31** + **32**)' were 0.39, 0.01, 6.07, and 1.18 μmol/L for ginsenosides Rb_1 (**1**), Rd (**2**), and Rg_1 (**31**), and notoginsenoside R_1 (**32**), respectively. Such concentrations (C_b) in panel b were 1.20, 0.09, 6.07, and 1.18 μmol/L, respectively, which were close to unbound C_{max} after the repeated doses of the injection on day 18. Panels c, d, e, and f are % inhibition of OATP1B3 over ginsenoside concentration by ginsenosides Rb_1 (**1**), Rd (**2**), and Rg_1 (**31**) and notoginsenoside R_1 (**32**), respectively.



Supplementary Fig. S3 Inductive effects of ginsenosides Rb_1 (**1**), Rd (**2**), and Rg_1 (**31**), notoginsenoside R_1 (**32**), and XueShuanTong (**XST**) on CYP1A2 activity (**a**–**c**), CYP2B6 activity (**d**–**f**), and CYP2B6 mRNA (**g**). These ginsenosides (**1**, **2**, **31**, and **32**) and XueShuanTong (**XST**) were tested at low, intermediate, and high concentrations (open, light blue, and blue bars, respectively), i.e., 1/10/100 µmol/L, except for ginsenoside Rd (**2**) at 0.1/1/10 µmol/L and XueShuanTong (**XST**) at the marker concentrations 1/10/100 µmol/L of ginsenoside Rg_1 (**31**) present. Cryopreserved human hepatocytes from three donors [XSM (**a**, **d**, **g**), HVN (**b**, **e**), and IZT (**c**, **f**)] were used; β-naphthoflavone and rifampin (both at 20 µmol/L; known inducers of CYP1A2 and CYP2B6, respectively) were used as positive controls (PC). The details of in vitro induction studies for CYP1A2 and CYP2B6 were similar to that for CYP3A, except for phenacetin and bupropion used as probe substrates of CYP1A2 and CYP2B6, respectively. Data are expressed as the mean ± standard deviation.