

**Metabolic profile of Yi-Xin-Shu capsule in rat by ultra performance
liquid chromatography coupled with quadrupole time-of-flight
tandem mass spectrometry analysis**

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Supplementary Data

Content S1 Identification of metabolites of YXS

A total of 62 YXS-related metabolites were tentatively identified in rat biofluids. According to the origins of parent compounds and structural types, all these metabolites were categorized as lignans-related, tanshinone-related and ginsenoside-related compounds (shown in Table S2). The prototype compounds were showed in Table S1.

1.1. Identification of lignans-related metabolites

Total 37 lignans-related metabolites were tentatively identified in rat biofluids by comparison with the literature or the fragmentation ions obtained from their MS/MS spectra. All of them were mainly generated from three parent compounds, including Schisandrin A, Schisandrin B and Schisantherin B. Total 11 metabolites, including **M1**, **M2**, **M4**, **M6-M8**, **M10**, **M12**, **M24**, **M26** and **M29** were firstly identified in this study.

M30 was tentatively identified as Schisandrin A metabolites, which were formed by losses of 2CH_2 . **M1**, **M2** and **M7** showed the precursor ion at m/z 419.1705 ($\text{C}_{22}\text{H}_{27}\text{O}_8$), 30 Da more than that of **M30**. The fragmentation ions at m/z 401.1570, 359.1480, 331.1166 and 316.0931 suggested that H_2O , C_3H_6 , CO and CH_3 were successively eliminated from $[\text{M}+\text{H}]^+$. The MFB from **M30** to **M1**, **M2** as well as **M7** is $-\text{H}_2+\text{O}_2$. Based on the data mentioned above, **M1**, **M2** and **M7** were demethylation to carboxylic acid metabolites of **M30**. The MS/MS spectrum of **M2** was shown in Fig. 2 (A). **M4**, **M8**, **M10** and **M12** were observed at m/z 417.1912 ($\text{C}_{23}\text{H}_{29}\text{O}_7$), 16 Da more than that of Schisandrin B. The fragmentation pathways of **M4**, **M8**, **M10** and

M12 were similar to that of Schisandrin B. Thus, **M4**, **M8**, **M10** and **M12** were oxidation metabolites of Schisandrin B. **M24** and **M26** gave the precursor ion at m/z 415.1755 ($C_{23}H_{27}O_7$), 14 Da more than that of Schisandrin B. The fragmentation ions at m/z 397.1583, 385.1667, 373.1772, 366.1451, 342.1080 and 327.1198 were formed by the individual or combined losses of H_2O , OCH_2 , C_3H_6 or OCH_3 . The MFB from Schisandrin B to **M24** as well as **M26** is $-H_2+O$. Thus, **M24** and **M26** were identified as methylene to Ketone metabolites of Schisandrin B. Similarly, **M6** was deduced as metabolite of Schisandrin B and was formed by the loss of CH_2 and di-oxidation. **M29** showed the precursor ion at m/z 485.2172 ($C_{27}H_{33}O_8$), 30 Da less than that of Schisantherin B. The fragmentation ion at m/z 401.1560, 383.1464, 352.1295 and 337.1067 indicating that C_6H_{12} , H_2O , OCH_3 and CH_3 were successively eliminated from $[M+H]^+$. Other fragmentation ions at m/z 371.1483, 341.1015 and 326.1128 were formed by the successively losses of OCH_2 , OCH_2 and CH_3 from $[M+H-C_6H_{12}]^+$. The MFB from Schisandrin B to **M29** is $-C-H_2-O$. Based on the data, we deduced **M29** was metabolite of Schisantherin B and was formed by the loss of OCH_2 .

1.2. Identification tanshinone-related metabolites

Total 17 tanshinone-related metabolites were tentatively identified in rat biofluids, shown in Table 2. The detected result suggested that the tanshinone-related metabolites were mainly generated from three parent compounds, including Cryptotanshinone, Tanshinone IIA and Tanshinone I.

M40-M42 and **M48** showed the precursor ion at m/z 313.1438 ($C_{19}H_{21}O_4$), 16 Da more than that of Cryptotanshinone. The fragmentation ions of **M40-M42** were

observed at m/z 285.1472, 267.1397 and 252.1150, which were formed via the successive losses of CO, H₂O and CH₃ from [M+H]⁺. The fragmentation ion at m/z 254.1301[M+H-CO-CH₂OH]⁺ indicated that there was a CH₂OH in the structure. Different from **M40-M42**, the fragmentation ions of **M48** were observed at m/z 295.1437, 277.1348 and 262.1104, which were formed via the successive losses of H₂O, H₂O and CH₃. The MFB from Cryptotanshinone to **M40-M42** as well as **M48** is +O. Thus, **M40-M42** and **M48** were deduced as Hydroxylation metabolites of Cryptotanshinone. The hydroxylation positions of **M40-M42** were CH₃ group while **M48** was CH₂ group. **M43**, **M46**, **M47** and **M51** showed the precursor ion at m/z 329.1387, 16 Da more than that of **M48**. Due to the fragmentation pathway was similar to that of **M48** and the MFB from **M48** to **M43**, **M46**, **M47** as well as **M51** is +O, we deduced that **M43**, **M46**, **M47** and **M51** were di-hydroxylation metabolites of Cryptotanshinone. Similarly, **M38** was deduced as tri-hydroxylation Cryptotanshinone due to it was 16 Da more than di-hydroxylation Cryptotanshinone and owned the same fragmentation pathway as **M43**, **M46**, **M47** and **M51**. The MS/MS spectrum was shown in Fig. 2(B).

M39 and **M45** gave the precursor ion at m/z 293.0816, 16 Da more than that of Tanshinone I. In their MS/MS spectra, the fragmentation ions were observed at m/z 265.1137, 234.0703 and 219.0817, indicating CO, CH₂OH and CH₃ were successively eliminated from [M+H]⁺. The MFB from Tanshinone I to them is +O. Based on the data, **M39** and **M45** were deduced as hydroxylation metabolites of Tanshinone I. **M50** gave the precursor ion at m/z 311.1281, 16 Da more than that of Tanshinone II A. In

the MS/MS spectra, the fragmentation ions were observed at m/z 283.1337, 265.1218, 250.0992 and 222.1018 indicating that H_2O , H_2O , CH_3 and CO were successively eliminated from $[M+H]^+$. The MFB from Tanshinone II A to **M50** is +O. Thus, **M50** was deduced as hydroxylation metabolite of Tanshinone II A. In the same way, **M42** was assigned as di-hydroxylation metabolite of Tanshinone II A. **M52** showed the precursor ion at m/z 293.1176, 2 Da less than that of Tanshinone II A. Due to the fragmentation pathway of **M52** was similar to that of Tanshinone II A, **M52** was deduced as dehydrogenation metabolite of Tanshinone II A. **M49** gave the precursor ion at m/z 327.1231, 16 Da more than that of Tanshinone II B. In the MS/MS spectra, the fragmentation ion at m/z 309.1124 and 281.1178 suggesting H_2O , CO were successively eliminated from $[M+H]^+$. The fragmentation ion at m/z 250.1091 $[M+H-H_2O-CO-CH_2OH]^+$ indicating that there is CH_2OH in the structure. The MFB from Tanshinone II B to **M49** is +O. Thus, **M49** was deduced as hydroxylation metabolite of Tanshinone II B.

1.3. Identification ginsenoside-related metabolites

10 ginsenoside-related metabolites were detected from the drug-containing plasma, feces samples as well as urine sample, shown in Table 2. The results suggested that almost all of the detected metabolites were secondary glycosides, which were formed by sequential deglycosylation metabolites in intestine. According to the structural types of ginsenosides, they were generally divided into three groups, including (20*S*)-protopanaxatriols type (Group I), (20*S*)-protopanaxadiols type (Group II) and oleananes type (Group III), which yielded the characteristic aglycone

ions at m/z 475.3787, 459.3848 and 455.3510, respectively.

Metabolites **M54** and **M58** yielded the characteristic aglycone ion at m/z 475.3817, indicating that they were (20*S*)-protopanaxatriols type ginsenosides. **M54** and **M58** were assigned as ginsenoside F₁ or its isomer as it showed the adduct ion at m/z 683.4382, which was 162 Da (Glc) more than that of aglycone ion. **M53** showed the deprotonated ion at m/z 1123.5893, 16 Da more than that of ginsenoside Rb₁. The fragmentation ions at m/z 961.5382, 799.4846, 637.4310 and 475.3780 were formed by the successive losses of Glc from [M-H]⁻. Due to **M53** was absent from YXS but presented in the rat biofluid, **M53** was deduced as metabolite of ginsenoside. The MFB from ginsenoside Rb₁ to **M53** is +O. Therefore, **M53** was assigned as oxidation metabolite of ginsenoside Rb₁.

Metabolites **M55-M57** and **M59** yielded the characteristic aglycone ion at m/z 459.3849, indicating that they were (20*S*)-protopanaxadiols type ginsenosides. The fragmentation pathways were similar to those of ginsenoside Rd. Thus, **M56**, **M57** and **M59** were tentatively deduced as Rd isomer.

Metabolites **M60-M62** yielded the characteristic aglycone ion at m/z 455.3525, indicating that they were oleananes type compounds. **M60** gave the deprotonated ion at m/z 793.4381, 162 Da less than ginsenoside Ro. After Glc being eliminated, the fragmentation pathway of ginsenoside Ro was similar to that of **M60**. Thus, **M60** was tentatively deduced as Glc removal metabolite of ginsenoside Ro. The MS/MS spectrum of **M60** was shown in Fig. 2(C). Similarly, **M61** and **M62** were tentatively deduced as 2Glc removal metabolites of ginsenoside Ro and Ro isomer, respectively.

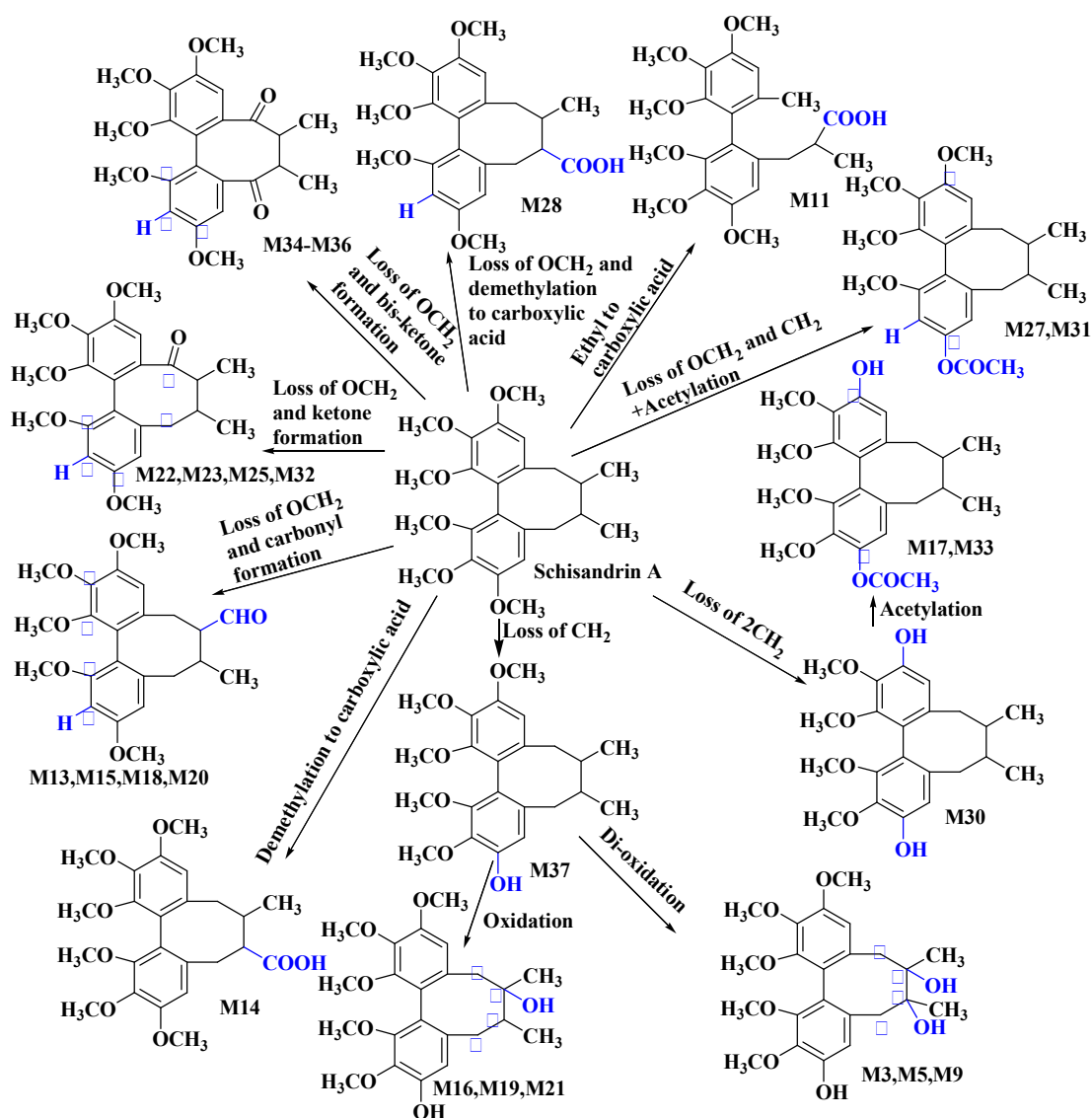


Fig. S1 The metabolic pathways of Schisandrins A.

Table S1 The prototype compounds detected in rat biofluids.

No.	t _R (min)	Molecular formula	Measured value (<i>m/z</i>) [M+H] ⁺	Diff (ppm)	Compound name	Source
<i>Prototype lignans</i>						
1	8.85	C ₂₈ H ₃₄ O ₁₀	548.2493 ^b	-0.55	Gomisin D isomer	P
2	9.37	C ₂₄ H ₃₂ O ₇	433.2223	-0.69	Schizandrol A ^a	P, U
3	9.63	C ₂₈ H ₃₄ O ₁₀	548.2501 ^b	0.91	Gomisin D	P, U, F
4	10.05	C ₂₄ H ₃₂ O ₇	433.2226	0	Schizandrol A isomer	P
5	10.15	C ₂₂ H ₂₈ O ₆	389.1962	-0.51	Gomisin J	F
6	10.34	C ₂₂ H ₂₈ O ₆	389.1963	-0.26	Gomisin J isomer	F
7	10.57	C ₂₉ H ₃₈ O ₉	548.2858 ^b	-0.36	Tigloyl gomisin Q/Angeloyl gomisin	P, F
8	10.72	C ₂₃ H ₂₈ O ₆	401.1967	0.75	Kadsuranin/isomer	U
9	10.97	C ₂₃ H ₂₈ O ₆	401.1966	0.50	Kadsuranin/isomer	P, U
10	10.98	C ₂₉ H ₃₈ O ₉	548.2861 ^b	0.18	Tigloyl gomisin Q/Angeloyl gomisin Q	P
11	11.24	C ₂₂ H ₂₈ O ₆	389.1966	0.51	Gomisin J isomer	F
12	11.24	C ₃₁ H ₃₆ O ₉	570.2708 ^b	0.88	Benzoyl isogomisin Q	P
13	11.37	C ₂₉ H ₃₈ O ₉	548.2865 ^b	0.91	Tigloyl gomisin Q isomer/Angeloyl gomisin Q isomer	P, F
14	11.80	C ₂₃ H ₃₀ O ₆	403.2118	-0.74	(-) Gomisin K ₁	F
15	11.95	C ₂₃ H ₃₀ O ₆	403.2117	-0.99	(+) Gomisin K ₂	F
16	12.04	C ₂₈ H ₃₄ O ₉	532.2548 ^b	0.19	Schisantherin B	P, U
17	12.20	C ₂₃ H ₃₀ O ₆	403.2120	-0.25	(-) Gomisin K ₁ isomer/(+) Gomisin K ₂ isomer	F
18	12.26	C ₂₄ H ₃₂ O ₆	554.2388 ^b	-0.36	Schisantherin A ^a	P, U
19	12.40	C ₂₈ H ₃₄ O ₉	532.2542 ^b	-0.94	Schisantherin B isomer	P, F
20	12.85	C ₂₃ H ₃₀ O ₆	403.2118	-0.74	Schisanhenol	U
21	13.50	C ₂₈ H ₃₄ O ₉	515.2286	0.97	Gomisin E	F
22	14.62	C ₂₄ H ₃₂ O ₆	417.2281	0.96	Schisandrin A ^a	P, F
23	15.16	C ₂₃ H ₂₈ O ₆	401.1965	0.25	Gomisin N	U
24	15.31	C ₂₃ H ₂₈ O ₆	401.1964	0	Schisandrin B ^a	P, F
<i>Prototype tanshinones</i>						
25	5.84	C ₁₈ H ₁₆ O ₅	313.1076	0	Tanshindiol B/Tanshindiol C	P, F
26	7.36	C ₁₉ H ₂₀ O ₄	313.1438	-0.64	1,2,6,7,8,9-Hexahydro-1,6,6-trimethyl-3,11-dioxanaphth[2,1-e]azulene-10,12-dione/isomer	P, F
27	7.80	C ₁₉ H ₂₀ O ₄	313.1437	-0.96	1β-Hydroxy cryptotanshinone	P, F
28	8.62	C ₁₈ H ₁₄ O ₄	295.0969	-0.34	1,2-Dihydro-1,6-dimethylfuro[3,2-c]naphth[2,1-e]oxepin-10,12-dione	P, F
29	8.77	C ₁₉ H ₁₈ O ₄	311.1280	-0.96	6,7,8,9-Tetrahydro-1,6,6-trimethylfuro[3,2-c]naphth[2,1-e]exepine-10,12-dione	P, F
30	8.92	C ₁₉ H ₁₈ O ₄	311.1281	-0.64	6,7,8,9-Tetrahydro-1,6,6-trimethylfuro[3,2-c]naphth[2,1-e]exepine-10,12-dione isomer	P, F
31	9.02	C ₁₉ H ₁₈ O ₄	311.1286	0.96	1-Oxo cryptotanshinone	P, F
32	9.10	C ₁₉ H ₁₈ O ₄	311.1279	-1.29	Tanshinone II B	P, F

33	9.20	C ₁₉ H ₁₈ O ₄	311.1281	-0.64	Hydroxytanshinone II A/3 α -Hydroxy tanshinone II A	P, F
34	9.60	C ₁₈ H ₁₆ O ₄	297.1128	0.34	Tanshinone VI	P, F
35	10.40	C ₁₈ H ₁₄ O ₃	279.1025	1.43	1,2-Dihydro-tanshinquinone I /15,16- Dihydrotanshinone	P, F
36	10.85	C ₁₈ H ₁₆ O ₃	281.1174	-1.42	Danshenxinkun B	P, F
37	11.22	C ₂₀ H ₁₈ O ₅	339.1231	-0.25	Methyl tanshinonate	P, F
38	12.32	C ₁₈ H ₁₂ O ₃	277.0860	-1.8	Tanshinone I ^a	P, F
39	12.45	C ₁₉ H ₂₀ O ₃	297.1489	-0.67	Cryptotanshinone ^a	P, F
40	13.83	C ₁₉ H ₁₆ O ₃	293.1180	0.68	Unknown	P, F
41	14.72	C ₁₉ H ₁₈ O ₃	295.1336	0.68	Tanshinone II A ^a	P, F
<i>Prototype ginsenosides</i>						
42	4.06	C ₅₄ H ₉₂ O ₂₃	1107.5926	-2.26	Unknown	P
43	4.18	C ₄₈ H ₈₂ O ₁₉	961.5382	1.04	Re ₃ ^a	P
44	4.21	C ₅₄ H ₉₂ O ₂₃	1107.5961	0.90	Unknown	P
45	4.36	C ₄₇ H ₈₀ O ₁₈	931.5275	0.97	Re ₄	P
46	4.40	C ₄₈ H ₈₂ O ₁₉	961.5358	-1.46	20-Gluco-ginsenoside Rf ^a	P
47	4.50	C ₄₇ H ₈₀ O ₁₈	931.5262	-0.43	Notoginsenoside R ₁ isomer	P
48	4.53	C ₄₈ H ₈₂ O ₁₉	961.5360	-1.25	Re ₁	P
49	4.58	C ₄₇ H ₈₀ O ₁₈	931.5275	0.97	Notoginsenoside R ₁ ^a	P
50	4.63	C ₄₈ H ₈₂ O ₁₉	961.5380	0.83	Re ₂	P
51	4.71	C ₅₄ H ₉₂ O ₂₃	1107.5954	0.27	Unknown	P
52	4.90	C ₄₈ H ₈₂ O ₁₈	945.5433	1.06	Re ^a	P, U, F
53	4.93	C ₄₂ H ₇₂ O ₁₄	799.4863	2.38	Rg ₁ ^a	P, U, F
54	5.30	C ₅₄ H ₉₂ O ₂₄	1123.5864	-3.20	Koryoginsenoside R ₂ isomer	P, F
55	5.38	C ₅₃ H ₉₀ O ₂₃	1093.5785	-0.91	Floralginsenoside P/isomer	P, F
56	5.46	C ₅₄ H ₉₂ O ₂₄	1123.5867	-2.94	Koryoginsenoside R ₂	F
57	5.60	C ₅₄ H ₉₂ O ₂₄	1123.5865	-3.12	Koryoginsenoside R ₂ isomer	F
58	5.63	C ₅₃ H ₉₀ O ₂₃	1093.5769	-2.38	Floralginsenoside P/isomer	P, F
59	5.75	C ₄₁ H ₇₀ O ₁₃	815.4806 ^c	1.59	Ginsenoside F ₃ /Ginsenoside F ₅	P
60	5.78	C ₅₃ H ₉₀ O ₂₃	1093.5776	-1.74	Floralginsenoside P/isomer	P, F
61	5.90	C ₅₃ H ₉₀ O ₂₃	1093.5770	-2.29	Floralginsenoside P/isomer	P
62	5.91	C ₄₈ H ₈₂ O ₁₉	961.5382	1.04	Notoginsenoside N isomer	P, F
63	6.10	C ₄₈ H ₈₂ O ₁₉	961.5367	-0.52	Notoginsenoside N	P, U, F
64	6.20	C ₄₈ H ₈₂ O ₁₉	961.5380	0.83	Vinaginsenoside R ₄	P, U, F
65	6.26	C ₆₀ H ₁₀₂ O ₂₈	1269.6467	-0.95	Unknown	F
66	6.50	C ₆₀ H ₁₀₂ O ₂₈	1269.6459	-1.58	Unknown	F
67	6.63	C ₄₂ H ₇₂ O ₁₄	799.4857	1.63	Rf isomer	P
68	6.78	C ₄₂ H ₇₂ O ₁₄	799.4866	2.75	Rf ^a	P, U, F
69	6.90	C ₆₀ H ₁₀₂ O ₂₈	1269.6444	-2.76	Unknown	F
70	6.93	C ₄₁ H ₇₀ O ₁₃	769.4767	3.77	Notoginsenoside R ₂ ^a	P
71	6.97	C ₅₈ H ₉₈ O ₂₆	1209.6230	-3.14	Ra ₂ ^a	P
72	7.00	C ₅₉ H ₁₀₀ O ₂₇	1239.6343	-2.50	Ra ₃ ^a	P
73	7.06	C ₅₄ H ₉₂ O ₂₃	1107.5965	1.26	Rb ₁ ^a	P, U, F

74	7.13	C ₄₈ H ₇₆ O ₁₉	955.4890	-1.36	Ro isomer	P
75	7.24	C ₄₂ H ₇₂ O ₁₃	783.4927	4.08	Rg ₂ ^a	P, U, F
76	7.27	C ₅₈ H ₉₈ O ₂₆	1209.6232	-2.98	Ra ₁ ^a	P
77	7.30	C ₅₃ H ₉₀ O ₂₂	1077.5852	0.65	Rc ^a	P, U, F
78	7.33	C ₄₂ H ₇₂ O ₁₃	783.4925	3.83	20(R)-Rg ₂ ^a	P, U, F
79	7.33	C ₄₈ H ₇₆ O ₁₉	955.4921	1.88	Ro ^a	P, U, F
80	7.38	C ₃₆ H ₆₂ O ₉	637.4326	1.57	Rh ₁ ^a	P, U, F
81	7.50	C ₄₈ H ₇₆ O ₁₉	955.4874	-3.04	Ro isomer	P, U, F
82	7.53	C ₅₃ H ₉₀ O ₂₂	1077.5847	0.19	Rb ₂ ^a	P, U, F
83	7.60	C ₅₃ H ₉₀ O ₂₂	1077.5841	-0.37	Rb ₃ ^a	P, U, F
84	7.78	C ₅₆ H ₉₄ O ₂₄	1149.6035	-1.91	Quinquenoside R ₁ ^a	P, U, F
85	7.78	C ₅₄ H ₉₂ O ₂₃	1107.5950	-0.09	Rb ₁ isomer	U, F
86	7.78	C ₄₇ H ₇₄ O ₁₈	925.4803	0.65	Pseudo-ginsenoside-RT ₁ /Chikusetsusaponin IV	U, F
87	8.03	C ₅₅ H ₉₂ O ₂₃	1119.5946	-0.45	Rs ₂ ^a	P
88	8.10	C ₄₈ H ₈₂ O ₁₈	945.5447	2.54	Rd ^a	P, U, F
89	8.16	C ₅₁ H ₈₄ O ₂₁	1031.5428	0.10	Malonyl-ginsenoside Rd	F
90	8.18	C ₅₆ H ₉₄ O ₂₄	1149.6034	-2.00	Quinquenoside R ₁ isomer	U
91	8.33	C ₄₄ H ₇₄ O ₁₄	825.5020	2.42	Acetyl-Rg ₂	U, F
92	8.45	C ₄₈ H ₈₂ O ₁₈	945.5430	0.74	Rd isomer	P, U, F
93	8.50	C ₅₀ H ₈₄ O ₁₉	987.5543	1.42	Acetyl-Rd/isomer	U, F
94	8.56	C ₄₉ H ₇₈ O ₁₉	1015.5110 ^c	-0.39	Ginsenoside Ro methyl ester ^a	P
95	8.66	C ₄₈ H ₈₂ O ₁₈	945.5415	-0.85	Gypenoside X VII	U, F
96	8.75	C ₄₇ H ₈₀ O ₁₇	915.5316	-0.11	Vinaginsenoside R ₁₆	P, U, F
97	8.81	C ₅₀ H ₈₄ O ₁₉	987.5555	2.63	Pseudo-ginsenoside RC ₁	U, F
98	8.86	C ₄₇ H ₈₀ O ₁₇	915.5326	0.98	Gypenoside IX	U, F
99	8.96	C ₄₇ H ₈₀ O ₁₇	961.5372 ^c	0	Notoginsenoside Fe	P, U, F
100	9.11	C ₅₀ H ₈₄ O ₁₉	987.5536	0.71	Acetyl-gypenoside X VII	U, F
101	9.18	C ₅₀ H ₈₄ O ₁₉	987.5531	0.20	Acetyl-gypenoside X VII isomer	U, F
102	9.46	C ₄₇ H ₇₄ O ₁₈	925.4829	3.46	Pseudo-ginsenoside-RT ₁ isomer/Chikusetsusaponin IV isomer	P
103	9.51	C ₄₂ H ₆₆ O ₁₄	793.4404	3.78	Chikusetsusaponin IVa ^a	P, U, F
104	9.63	C ₄₂ H ₇₂ O ₁₃	783.4926	3.96	Ginsenoside F ₂	P, U, F
105	10.09	C ₄₂ H ₇₂ O ₁₃	783.4895	0	Rg ₃ ^a	P, U, F
106	10.16	C ₄₂ H ₇₂ O ₁₃	783.4920	3.19	(20R)-Rg ₃ ^a	P, U, F
107	11.12	C ₄₄ H ₇₄ O ₁₄	871.5062 ^c	0.80	Acetyl-(S/R)-Rg ₃ /isomer	U, F
108	11.32	C ₄₄ H ₇₄ O ₁₄	871.5063 ^c	0.92	Acetyl-(S/R)-Rg ₃ /isomer	U, F
109	11.90	C ₆₅ H ₁₀₀ O ₂₁	1215.6633	-3.78	Polyacetyleneginsenoside-Ro/isomer	U, F
110	12.12	C ₆₅ H ₁₀₀ O ₂₁	1215.6639	-3.29	Polyacetyleneginsenoside-Ro/isomer	U, F
111	13.35	C ₃₆ H ₆₂ O ₈	667.4445 ^c	3.60	Rh ₂ ^a	U, F
112	13.52	C ₃₆ H ₆₂ O ₈	667.4443 ^c	3.30	20(R)-Rh ₂ ^a	U, F
<i>Prototype flavonoids</i>						
113	2.99	C ₂₁ H ₂₀ O ₁₀	433.1147	2.77	Vitexin ^a	U
114	5.36	C ₁₆ H ₁₂ O ₅	285.0749	-4.91	Calycosin	U, F
<i>Prototype lactones</i>						

115	7.33	C ₁₂ H ₁₂ O ₂	189.0911	-2.64	3-Butylidenephthalide	P, U, F
116	14.41	C ₁₂ H ₁₂ O ₃	205.0861	-1.95	Senkyunolide B/C/E	P, U, F
<i>Prototype phenolicacids and triterpenoid acid</i>						
117	4.10	C ₂₆ H ₂₂ O ₁₀	493.1151	3.24	Salvianolic acid A	U, F
118	4.45	C ₃₆ H ₃₀ O ₁₆	717.1466	1.39	Salvianolic acid B	U, F
119	11.72	C ₃₀ H ₄₈ O ₃	455.3529	0.88	Ursolic acid/Oleanlic acid	U, F
<i>Prototype astragalus saponins</i>						
120	6.66	C ₄₁ H ₇₀ O ₁₄	785.4726	4.96	Cyclocanthoside E	U, F
121	7.41	C ₄₇ H ₇₈ O ₁₉	991.5133 ^c	1.92	Astragaloside V/Astragaloside VI/AstragalosideVII	U, F
122	7.88	C ₄₁ H ₆₈ O ₁₄	829.4621 ^c	4.22	Astragaloside IV ^a	P, U, F

a: The compounds were identified by comparison with the reference standards; *b*: [M+NH₄]⁺; *c*: [M+HCOO]⁻.

Table S2 The metabolites detected in rat biofluids.

No.	t _R (min)	Molecular formula	Measured value (<i>m/z</i>) [M+H] ⁺	Diff (ppm)	Product ions	Compound name	Source
<i>Lignans-related metabolites</i>							
M1	5.33	C ₂₂ H ₂₆ O ₈	419.1705	-0.23	401.1697[M+H-H ₂ O] ⁺ , 386.1470[M+H-H ₂ O-CH ₃] ⁺ , 359.1595[M+H-H ₂ O-C ₃ H ₆] ⁺ , 344.1353[M+H-H ₂ O-C ₃ H ₆ -CH ₃] ⁺ , 331.1283[M+H-H ₂ O-C ₃ H ₆ -CO] ⁺ , 316.1050[M+H-H ₂ O-C ₃ H ₆ -CO-CH ₃] ⁺	Schisandrin A 2CH ₂ +demmet hylation to carboxylic acid	P, U
M2	5.37	C ₂₂ H ₂₆ O ₈	419.1697	0.6	401.1570[M+H-H ₂ O] ⁺ , 386.1314[M+H-H ₂ O-CH ₃] ⁺ , 359.1480[M+H-H ₂ O-C ₃ H ₆] ⁺ , 355.1138[M+H-H ₂ O-CH ₃ -OCH ₃] ⁺ , 331.1166[M+H-H ₂ O-C ₃ H ₆ -CO] ⁺ , 316.0931[M+H-H ₂ O-C ₃ H ₆ -CO-CH ₃] ⁺ , 303.0851[M+H-H ₂ O-C ₃ H ₆ -CO-C ₂ H ₄] ⁺	Schisandrin A loss of 2CH ₂ +demmet hylation to carboxylic acid	P, F
M3	5.57	C ₂₃ H ₃₀ O ₈	435.2017	-0.46	417.1994[M+H-H ₂ O] ⁺ , 399.1784[M+H-2H ₂ O] ⁺ , 386.1680[M+H-H ₂ O-OCH ₃] ⁺ , 355.1805[M+H-H ₂ O-2OCH ₃] ⁺ , 327.1198[M+H-H ₂ O-2OCH ₃ -C ₂ H ₄] ⁺	Schisandrin A loss of CH ₂ +di- oxidation	P
M4	5.73	C ₂₃ H ₂₈ O ₇	417.1912	-0.72	399.1909[M+H-H ₂ O] ⁺ , 386.1819[M+H-OCH ₃] ⁺ , 368.1697[M+H-H ₂ O-OCH ₃] ⁺ , 359.1581[M+H-H ₂ O-C ₂ H ₄ O] ⁺ , 344.1361[M+H-H ₂ O-C ₂ H ₄ O-CH ₃] ⁺ , 328.1391[M+H-H ₂ O-C ₂ H ₄ O-OCH ₃] ⁺	Schisandrin B oxidation	P, U
M5	5.76	C ₂₃ H ₃₀ O ₈	435.2016	-0.69	417.1948[M+H-H ₂ O] ⁺ , 399.1678[M+H-2H ₂ O] ⁺ , 386.1643[M+H-H ₂ O-OCH ₃] ⁺ , 355.1133[M+H-H ₂ O-2OCH ₃] ⁺ , 327.1200[M+H-H ₂ O-2OCH ₃ -C ₂ H ₄] ⁺	Schisandrin A loss of CH ₂ +di- oxidation	P
M6	6.12	C ₂₂ H ₂₆ O ₈	419.1706	0	401.1556[M+H-H ₂ O] ⁺ , 388.1477[M+H-OCH ₃] ⁺ , 345.1413[M+H-H ₂ O-C ₄ H ₈] ⁺ , 327.1321[M+H-2H ₂ O-C ₄ H ₈] ⁺ , 296.1146[M+H-2H ₂ O-C ₄ H ₈ -OCH ₃] ⁺ , 281.0930[M+H-2H ₂ O-C ₄ H ₈ -OCH ₃ - CH ₃] ⁺	Schisandrin B loss of CH ₂ +di- oxidation	P, U
M7	6.15	C ₂₂ H ₂₆ O ₈	419.1697	0.6	401.1572[M+H-H ₂ O] ⁺	Schisandrin A	P, F

					386.1462[M+H-H ₂ O-CH ₃] ⁺ , 359.1480[M+H-H ₂ O-C ₃ H ₆] ⁺ , 355.1262[M+H-H ₂ O-CH ₃ -OCH ₃] ⁺ , 331.1167[M+H-H ₂ O-C ₃ H ₆ -C ₂ H ₄] ⁺ , 316.0944[M+H-H ₂ O-C ₃ H ₆ -C ₂ H ₄ - CH ₃] ⁺	loss of 2CH ₂ +demmet hylation to carboxylic acid	
M8	6.17	C ₂₃ H ₂₈ O ₇	417.1915	0.48	399.1909[M+H-H ₂ O] ⁺ , 386.1746[M+H-OCH ₃] ⁺ , 368.1697[M+H-H ₂ O-OCH ₃] ⁺ , 344.1361[M+H-H ₂ O-OCH ₃ -C ₃ H ₆] ⁺	Schisandrin B oxidation	P, F
M9	6.19	C ₂₃ H ₃₀ O ₈	435.2017	-0.46	417.1915[M+H-H ₂ O] ⁺ , 402.1791[M+H-H ₂ O-CH ₃] ⁺ , 399.1848[M+H-2H ₂ O] ⁺ , 386.1784[M+H-H ₂ O-OCH ₃] ⁺ , 368.1632[M+H-2H ₂ O-OCH ₃] ⁺ , 344.1346[M+H-H ₂ O-OCH ₃ -C ₃ H ₆] ⁺	Schisandrin A loss of CH ₂ +di- oxidation	P, U
M10	6.32	C ₂₃ H ₂₈ O ₇	417.1911	-0.48	399.1923[M+H-H ₂ O] ⁺ , 386.1743[M+H-OCH ₃] ⁺ , 368.1690[M+H-H ₂ O-OCH ₃] ⁺ , 344.1318[M+H-H ₂ O-OCH ₃ -C ₃ H ₆] ⁺	Schisandrin B oxidation	P, U
M11	6.45	C ₂₃ H ₂₈ O ₈	433.1863	0.23	415.1829[M+H-H ₂ O] ⁺ , 387.1893[M+H-HCOOH] ⁺ , 384.1637[M+H-H ₂ O-OCH ₃] ⁺ , 369.1428[M+H-H ₂ O-OCH ₃ -CH ₃] ⁺ , 345.1425[M+H-H ₂ O-CO-C ₃ H ₆] ⁺ , 330.1213[M+H-H ₂ O-CO-C ₃ H ₆ -CH ₃] ⁺ , 317.1127[M+H-H ₂ O-CO-C ₃ H ₆ -] ⁺	Schisandrin A ethyl to carboxylic acid	P, U
M12	6.50	C ₂₃ H ₂₈ O ₇	417.1909	-0.96	399.1919[M+H-H ₂ O] ⁺ , 386.1529[M+H-OCH ₃] ⁺ , 368.1657[M+H-H ₂ O-OCH ₃] ⁺ , 359.1538[M+H-H ₂ O-C ₂ H ₄ O] ⁺ , 344.1331[M+H-H ₂ O-C ₂ H ₄ O-CH ₃] ⁺ , 328.1385[M+H-H ₂ O-C ₂ H ₄ O-OCH ₃] ⁺	Schisandrin B oxidation	P, U
M13	7.36	C ₂₃ H ₂₈ O ₆	401.1963	-0.25	386.1890[M+H-CH ₃] ⁺ , 371.1744[M+H-2CH ₃] ⁺ , 355.1496[M+H-CH ₃ -OCH ₃] ⁺ , 337.1421[M+H-CH ₃ -OCH ₃ -H ₂ O] ⁺	Schisandrin A loss of OCH ₂ +carbony l formation	P
M14	7.61	C ₂₄ H ₃₀ O ₈	447.2023	0.89	429.2250[M+H-H ₂ O] ⁺ , 401.1819[M+H-H ₂ O-CO] ⁺ , 386.1743[M+H-H ₂ O-CO-CH ₃] ⁺ , 370.1819[M+H-H ₂ O-CO-OCH ₃] ⁺ , 356.1636[M+H-H ₂ O-CO-CH ₃ -OCH ₃] ⁺	Schisandrin A demethylation to carboxylic acid	P
M15	7.66	C ₂₃ H ₂₈ O ₆	401.1964	0	386.1891[M+H-CH ₃] ⁺ , 371.1732[M+H-2CH ₃] ⁺	Schisandrin A loss of	P

M16	7.66	C ₂₃ H ₃₀ O ₇	419.2071	0.24	355.1538[M+H-CH ₃ -OCH ₃] ⁺ , 337.1420[M+H-CH ₃ -OCH ₃ -H ₂ O] ⁺ 401.1932[M+H-H ₂ O] ⁺ , 386.1755[M+H-H ₂ O-CH ₃] ⁺ , 370.1745[M+H-H ₂ O-OCH ₃] ⁺ , 355.1537[M+H-H ₂ O-OCH ₃ -CH ₃] ⁺ , 337.1396[M+H-2H ₂ O-OCH ₃ -CH ₃] ⁺	OCH ₂ +carbonyl formation Schisandrin A loss of CH ₂ +oxidation	P
M17	7.77	C ₂₄ H ₃₀ O ₇	431.2064	-0.04	413.1981[M+H-H ₂ O] ⁺ , 400.1685[M+H-OCH ₃] ⁺ , 382.1745[M+H-H ₂ O-OCH ₃] ⁺ , 373.1604[M+H-OCOCH ₂] ⁺ , 358.1413[M+H-OCOCH ₂ -CH ₃] ⁺ , 342.1423[M+H-OCOCH ₂ -OCH ₃] ⁺ , 327.1211[M+H-OCOCH ₂ -OCH ₃ - CH ₃] ⁺	Schisandrin A loss of 2CH ₂ +acetylation	P, U
M18	7.82	C ₂₃ H ₂₈ O ₆	401.1961	-0.75	386.1712[M+H-CH ₃] ⁺ , 370.1862[M+H-OCH ₃] ⁺ , 355.1657[M+H-CH ₃ -OCH ₃] ⁺ , 337.1533[M+H-CH ₃ -OCH ₃ -H ₂ O] ⁺	Schisandrin A loss of OCH ₂ +carbonyl formation	P
M19	7.84	C ₂₃ H ₃₀ O ₇	419.2070	0	401.1930[M+H-H ₂ O] ⁺ , 386.1700[M+H-H ₂ O-CH ₃] ⁺ , 370.1745[M+H-H ₂ O-OCH ₃] ⁺ , 355.1527[M+H-H ₂ O-OCH ₃ -CH ₃] ⁺ , 337.1390[M+H-2H ₂ O-OCH ₃ -CH ₃] ⁺	Schisandrin A loss of CH ₂ +oxidation	P
M20	7.97	C ₂₃ H ₂₈ O ₆	401.1960	-0.98	386.1770[M+H-CH ₃] ⁺ , 371.1848[M+H-2CH ₃] ⁺ , 355.1563[M+H-CH ₃ -OCH ₃] ⁺ , 337.1556[M+H-CH ₃ -OCH ₃ -H ₂ O] ⁺	Schisandrin A loss of OCH ₂ +carbonyl formation	P
M21	7.99	C ₂₃ H ₃₀ O ₇	419.2070	0	401.1930[M+H-H ₂ O] ⁺ , 386.1755[M+H-H ₂ O-CH ₃] ⁺ , 370.1776[M+H-H ₂ O-OCH ₃] ⁺ , 355.1572[M+H-CH ₃ -H ₂ O-OCH ₃] ⁺ , 337.1426[M+H-2H ₂ O-OCH ₃ -CH ₃] ⁺	Schisandrin A loss of CH ₂ +oxidation	P
M22	8.11	C ₂₃ H ₂₈ O ₆	401.1963	-0.25	386.1710[M+H-CH ₃] ⁺ , 370.1749[M+H-OCH ₃] ⁺ , 355.1544[M+H-CH ₃ -OCH ₃] ⁺ , 337.1534[M+H-CH ₃ -OCH ₃ -H ₂ O] ⁺ , 332.1256[M+H-CH ₃ -C ₄ H ₆] ⁺	Schisandrin A loss of OCH ₂ +ketone formation	P
M23	8.24	C ₂₃ H ₂₈ O ₆	401.1960	-0.98	386.1687[M+H-CH ₃] ⁺ , 370.1743[M+H-OCH ₃] ⁺ , 355.1511[M+H-CH ₃ -OCH ₃] ⁺ , 337.1530[M+H-CH ₃ -OCH ₃ -H ₂ O] ⁺ , 332.1250[M+H-CH ₃ -C ₄ H ₆] ⁺	Schisandrin A loss of OCH ₂ +ketone formation	P
M24	8.28	C ₂₃ H ₂₆ O ₇	415.1755	-0.48	397.1583[M+H-H ₂ O] ⁺	Schisandrin B	P

					385.1667[M+H-OCH ₂] ⁺ , 373.1772[M+H-C ₃ H ₆] ⁺ , 366.1451[M+H-H ₂ O-OCH ₃] ⁺ , 342.1080[M+H-C ₃ H ₆ -OCH ₃] ⁺ , 327.1198[M+H-C ₃ H ₆ -OCH ₃ -CH ₃] ⁺	methylene to Ketone	
M25	8.41	C ₂₃ H ₂₈ O ₆	401.1970	0.75	386.1680[M+H-CH ₃] ⁺ , 370.1733[M+H-OCH ₃] ⁺ , 355.1510[M+H-CH ₃ -OCH ₃] ⁺ , 337.1533[M+H-CH ₃ -OCH ₃ -H ₂ O] ⁺ , 332.1253[M+H-CH ₃ -C ₄ H ₆] ⁺	Schisandrin A loss of OCH ₂ +bis- ketone formation	P
M26	8.51	C ₂₃ H ₂₆ O ₇	415.1755	-0.48	397.1576[M+H-H ₂ O] ⁺ , 385.1660[M+H-OCH ₂] ⁺ , 373.1771[M+H-C ₃ H ₆] ⁺ , 366.1455[M+H-H ₂ O-OCH ₃] ⁺ , 342.1090[M+H-C ₃ H ₆ -OCH ₃] ⁺ , 327.1148[M+H-C ₃ H ₆ -OCH ₃ -CH ₃] ⁺	Schisandrin B methylene to Ketone	P
M27	9.39	C ₂₄ H ₃₀ O ₆	415.2121	0	400.1875[M+H-CH ₃] ⁺ , 384.1934[M+H-OCH ₃] ⁺ , 369.1693[M+H-OCH ₃ -CH ₃] ⁺ , 353.1727[M+H-2OCH ₃] ⁺ , 342.1461[M+H-COOCH ₂] ⁺ , 338.1505[M+H-2OCH ₃ -CH ₃] ⁺	Schisandrin A loss of OCH ₂ and CH ₂ +acetylation	P, U
M28	9.60	C ₂₂ H ₂₆ O ₆	387.1806	-0.52	372.1775[M+H-CH ₃] ⁺ , 356.1666[M+H-OCH ₃] ⁺ , 341.1418[M+H-OCH ₃ -CH ₃] ⁺ , 323.1406[M+H-OCH ₃ -CH ₃ -H ₂ O] ⁺ , 295.1440[M+H-OCH ₃ -CH ₃ -H ₂ O-CO] ⁺	Schisandrin A loss of 2OCH ₂ +demet hylation to carboxylic acid	P, F
M29	9.68	C ₂₇ H ₃₂ O ₈	485.2172	-0.54	454.1706[M+H-OCH ₃] ⁺ , 426.1600[M+H-OCH ₃ -C ₂ H ₄] ⁺ , 401.1560[M+H-C ₆ H ₁₂] ⁺ , 383.1464[M+H-C ₆ H ₁₂ -H ₂ O] ⁺ , 371.1483[M+H-C ₆ H ₁₂ -OCH ₂] ⁺ , 352.1295[M+H-C ₆ H ₁₂ -H ₂ O-OCH ₃] ⁺ , 341.1015[M+H-C ₆ H ₁₂ -2OCH ₂] ⁺ , 337.1067[M+H-C ₆ H ₁₂ -H ₂ O-OCH ₃ - CH ₃] ⁺ , 326.1128[M+H-C ₆ H ₁₂ -2OCH ₂ -CH ₃] ⁺	Schisantherin B -OCH ₂	P, U
M30	10.13	C ₂₂ H ₂₈ O ₆	389.1961	-0.77	374.1799[M+H-CH ₃] ⁺ , 358.1874[M+H-OCH ₃] ⁺ , 343.1460[M+H-OCH ₃ -CH ₃] ⁺ , 319.2025[M+H-C ₅ H ₁₀] ⁺ , 288.1084[M+H-C ₅ H ₁₀ -OCH ₃] ⁺ , 273.0863[M+H-C ₅ H ₁₀ -OCH ₃ -CH ₃] ⁺	Schisandrin A loss of 2CH ₂	P, F
M31	10.23	C ₂₄ H ₃₀ O ₆	415.2117	-0.69	400.1865[M+H-CH ₃] ⁺	Schisandrin A	P, U

					384.1924[M+H-OCH ₃] ⁺ , 369.1690[M+H-OCH ₃ -CH ₃] ⁺ , 353.1737[M+H-2OCH ₃] ⁺ , 342.1456 [M+H-COOCH ₂] ⁺ , 338.1500[M+H-2OCH ₃ -CH ₃] ⁺	loss of OCH ₂ and CH ₂ +acetylation		
M32	10.80	C ₂₃ H ₂₈ O ₆	401.1967	0.75	386.1713[M+H-CH ₃] ⁺ , 370.1866[M+H-OCH ₃] ⁺ , 355.1648[M+H-CH ₃ -OCH ₃] ⁺ , 337.1537[M+H-CH ₃ -OCH ₃ -H ₂ O] ⁺ , 332.1254[M+H-CH ₃ -C ₄ H ₆] ⁺	Schisandrin A loss of OCH ₂ +ketone formation	P, U	
M33	11.43	C ₂₄ H ₃₀ O ₇	431.2067	-0.71	413.2003[M+H-H ₂ O] ⁺ , 400.1863[M+H-OCH ₃] ⁺ , 382.1785[M+H-H ₂ O-OCH ₃] ⁺ , 373.1614[M+H-OCOCH ₂] ⁺ , 358.1437[M+H-OCOCH ₂ -CH ₃] ⁺ , 342.1442[M+H-OCOCH ₂ -OCH ₃] ⁺ , 327.1222[M+H-OCOCH ₂ -OCH ₃ - CH ₃] ⁺	Schisandrin A loss of 2CH ₂ +acetylation	P	
M34	12.11	C ₂₃ H ₂₆ O ₇	415.1752	-0.31	400.1735[M+H-CH ₃] ⁺ , 385.1607[M+H-OCH ₂] ⁺ , 371.1476[M+H-C ₃ H ₆] ⁺ , 356.1259[M+H-C ₃ H ₆ -CH ₃] ⁺ , 340.1301[M+H-C ₃ H ₆ -OCH ₃] ⁺ , 325.1073[M+H-C ₃ H ₆ -OCH ₃ -CH ₃] ⁺	Schisandrin A loss of OCH ₂ +bis- ketone formation	P, U	
M35	12.37	C ₂₃ H ₂₆ O ₇	415.1755	-0.48	385.1759[M+H-OCH ₂] ⁺ , 371.1600[M+H-C ₃ H ₆] ⁺ , 356.1359[M+H-C ₃ H ₆ -CH ₃] ⁺ , 340.1410[M+H-C ₃ H ₆ -OCH ₃] ⁺ , 325.1177[M+H-C ₃ H ₆ -OCH ₃ -CH ₃] ⁺	Schisandrin A loss of OCH ₂ +bis- ketone formation	P, U	
M36	12.50	C ₂₃ H ₂₆ O ₇	415.1755	-0.77	400.1765[M+H-CH ₃] ⁺ , 385.1632[M+H-OCH ₂] ⁺ , 371.1480[M+H-C ₃ H ₆] ⁺ , 356.1259[M+H-C ₃ H ₆ -CH ₃] ⁺ , 340.1306[M+H-C ₃ H ₆ -OCH ₃] ⁺ , 325.1066[M+H-C ₃ H ₆ -OCH ₃ -CH ₃] ⁺	Schisandrin A loss of OCH ₂ +bis- ketone formation	P, U	
M37	12.94	C ₂₃ H ₃₀ O ₆	403.2113	0.63	388.1873[M+H-CH ₃] ⁺ , 372.1923[M+H-OCH ₃] ⁺ , 357.1673[M+H-CH ₃ -OCH ₃] ⁺ , 302.1137[M+H-OCH ₃ -C ₅ H ₁₀] ⁺ , 287.0890[M+H-OCH ₃ -C ₅ H ₁₀ -CH ₃] ⁺ , 271.0953[M+H-2OCH ₃ -C ₅ H ₁₀] ⁺	Schisandrin A loss of CH ₂	P	
<i>Tashinone-related metabolites</i>								
M38	6.34	C ₁₉ H ₂₀ O ₆	345.1335	-0.87	327.1267[M+H-H ₂ O] ⁺ , 309.1068[M+H-2H ₂ O] ⁺	Tri- hydroxylation	P, F	

					299.1256[M+H-H ₂ O-CO] ⁺ , 281.1166[M+H-2H ₂ O-CO] ⁺ , 263.1067[M+H-3H ₂ O-CO] ⁺ , 235.1113[M+H-3H ₂ O-2CO] ⁺	cryptotanshino ne	
M39	6.43	C ₁₈ H ₁₂ O ₄	293.0816	0.68	278.1529[M+H-CH ₃] ⁺ , 265.1137[M+H-CO] ⁺ , 234.0703[M+H-CO-CH ₂ OH] ⁺ , 219.0817[M+H-CO-CH ₂ OH-CH ₃] ⁺	Hydroxylation tanshinone I	P, F
M40	6.46	C ₁₉ H ₂₀ O ₄	313.1438	-0.64	285.1472[M+H-CO] ⁺ , 267.1397[M+H-CO-H ₂ O] ⁺ , 254.1301[M+H-CO-CH ₂ OH] ⁺ , 252.1150[M+H-CO-H ₂ O-CH ₃] ⁺	Hydroxylation cryptotanshino ne	P, F
M41	6.55	C ₁₉ H ₂₀ O ₄	313.1437	-0.96	285.1513[M+H-CO] ⁺ , 267.1380[M+H-CO-H ₂ O] ⁺ , 254.1293[M+H-CO-CH ₂ OH] ⁺ , 252.1143[M+H-CO-H ₂ O-CH ₃] ⁺	Hydroxylation cryptotanshino ne	P, F
M42	6.63	C ₁₉ H ₂₀ O ₄	313.1438	-0.64	285.1460[M+H-CO] ⁺ , 267.1371[M+H-CO-H ₂ O] ⁺ , 254.1281[M+H-CO-CH ₂ OH] ⁺ , 252.1147[M+H-CO-H ₂ O-CH ₃] ⁺	Hydroxylation cryptotanshino ne	P, F
M43	6.63	C ₁₉ H ₂₀ O ₅	329.1387	-0.61	311.1268 [M+H-H ₂ O] ⁺ , 283.1328[M+H-H ₂ O-CO] ⁺ , 265.1239[M+H-2H ₂ O-CO] ⁺ , 250.0988[M+H-2H ₂ O-CO-CH ₃] ⁺ , 237.1265 [M+H-2H ₂ O-2CO] ⁺	Di- hydroxylation cryptotanshino ne	P, F
M44	7.18	C ₁₉ H ₁₈ O ₅	327.1232	0	309.1108[M+H-H ₂ O] ⁺ , 281.1167[M+H-H ₂ O-CO] ⁺ , 250.0978[M+H-H ₂ O-CO-CH ₂ OH] ⁺	Di- hydroxylation tanshinone IIA	P, F
M45	7.39	C ₁₈ H ₁₂ O ₄	293.0807	-0.34	278.0876[M+H-CH ₃] ⁺ , 265.0784[M+H-CO] ⁺ , 234.0679[M+H-CO-CH ₂ OH] ⁺ , 219.0801[M+H-CO-CH ₂ OH-CH ₃] ⁺	Hydroxylation tanshinone I	P, F
M46	8.99	C ₁₉ H ₂₀ O ₅	329.1382	-2.13	311.1270[M+H-H ₂ O] ⁺ , 283.1323[M+H-H ₂ O-CO] ⁺ , 265.1226[M+H-2H ₂ O-CO] ⁺ , 250.0989[M+H-2H ₂ O-CO-CH ₃] ⁺ , 237.1245 [M+H-2H ₂ O-2CO] ⁺	Di- hydroxylation cryptotanshino ne	P, F
M47	9.34	C ₁₉ H ₂₀ O ₅	329.1383	-2.13	311.1273[M+H-H ₂ O] ⁺ , 283.1320[M+H-H ₂ O-CO] ⁺ , 265.1229[M+H-2H ₂ O-CO] ⁺ , 250.0998[M+H-2H ₂ O-CO-CH ₃] ⁺ , 237.1255 [M+H-2H ₂ O-2CO] ⁺	Di- hydroxylation cryptotanshino ne	P, F
M48	9.50	C ₁₉ H ₂₀ O ₄	313.1439	-0.32	295.1437[M+H-H ₂ O] ⁺ , 277.1348[M+H-2H ₂ O] ⁺	Hydroxylation cryptotanshino	P, F

					262.1104[M+H-2H ₂ O-CH ₃] ⁺ , 249.1400[M+H-2H ₂ O-CO] ⁺	ne	
M49	9.57	C ₁₉ H ₁₈ O ₅	327.1231	-0.31	309.1124[M+H-H ₂ O] ⁺ , 291.1021[M+H-2H ₂ O] ⁺ , 281.1178[M+H-H ₂ O-CO] ⁺ , 250.1091[M+H-H ₂ O-CO-CH ₂ OH] ⁺	Hydroxyl tashinone IIB	P, F
M50	10.30	C ₁₉ H ₁₈ O ₄	311.1281	-0.64	283.1337[M+H-H ₂ O] ⁺ , 265.1218[M+H-2H ₂ O] ⁺ , 250.0992[M+H-2H ₂ O-CH ₃] ⁺ , 237.1274[M+H-2H ₂ O-CO] ⁺ , 222.1018[M+H-2H ₂ O-CO-CH ₃] ⁺	Hydroxylation tanshinone II A	P, F
M51	10.31	C ₁₉ H ₂₀ O ₅	329.1384	-2.13	311.1298[M+H-H ₂ O] ⁺ , 283.1324[M+H-H ₂ O-CO] ⁺ , 265.1219[M+H-2H ₂ O-CO] ⁺ , 250.0998[M+H-2H ₂ O-CO-CH ₃] ⁺ , 237.1268[M+H-2H ₂ O-2CO] ⁺	Di- hydroxylation cryptotanshino ne	P, F
M52	12.99	C ₁₉ H ₁₆ O ₃	293.1176	-0.68	278.0967[M+H-CH ₃] ⁺ , 275.1138[M+H-H ₂ O] ⁺ , 263.0684[M+H-2CH ₃] ⁺ , 260.0858[M+H-CH ₃ -H ₂ O] ⁺ , 247.1094[M+H-H ₂ O-CO] ⁺ , 232.0931[M+H-H ₂ O-CO-CH ₃] ⁺	Dehydrogenati on tanshinone II A	P, F
<i>Ginsenosides-related metabolites</i>							
M53	5.68	C ₅₄ H ₉₂ O ₂₄	1123.5893	-0.62	961.5382[M-H-Glc] ⁻ , 799.4846[M-H-2Glc] ⁻ , 637.4310[M-H-3Glc] ⁻ , 475.3780[M-H-4Glc] ⁻	Monooxyg enated Rb ₁	P, U
M54	7.58	C ₃₆ H ₆₂ O ₉	683.4382 ^a	1.76	475.3817[M-H-Glc] ⁻	F ₁ /isomer	P
M55	7.64	C ₅₄ H ₉₂ O ₂₃	1107.5951	0	945.5405[M-H-Glc] ⁻ , 783.4812[M-H-2Glc] ⁻ , 621.4267[M-H-3Glc] ⁻ , 459.3849[M-H-4Glc] ⁻	Ra ₃ -Xyl	P, U, F
M56	9.13	C ₄₈ H ₈₂ O ₁₈	945.5438	1.59	783.4793 [M-H-Glc] ⁻ , 621.4172[M-H-2Glc] ⁻ , 459.3710[M-H-3Glc] ⁻	Rd isomer	P, U, F
M57	9.25	C ₄₈ H ₈₂ O ₁₈	945.5433	1.06	783.4795 [M-H-Glc] ⁻ , 621.4192[M-H-2Glc] ⁻ , 459.3715[M-H-3Glc] ⁻	Rd isomer	U, F
M58	9.33	C ₃₆ H ₆₂ O ₉	683.4386 ^a	2.34	475.3681[M-H-Glc] ⁻	F ₁ /isomer	P, U, F
M59	9.37	C ₄₈ H ₈₂ O ₁₈	991.5485 ^a	0.71	783.4799[M-H-Glc] ⁻ , 621.4285[M-H-2Glc] ⁻ , 459.3772[M-H-3Glc] ⁻	Rd isomer	U, F
M60	9.88	C ₄₂ H ₆₆ O ₁₄	793.4381	0.88	613.3840[M-H-Glc] ⁻ , 569.3850[M-H-Glc-CO ₂ -H ₂ O] ⁻	Ro-Glc	P, U, F

					551.3734[M-H-Glc-CO ₂ -2H ₂ O] ⁻ ,		
					455.3525[M-H-Glc-Glu A] ⁻		
M61	10.82	C ₃₆ H ₅₆ O ₉	631.3850	0.63	455.3584[M-H-Glu A] ⁻	Ro-2Glc	P, U, F
M62	11.81	C ₃₆ H ₅₆ O ₉	631.3862	2.53	455.3571[M-H-Glu A] ⁻	Ro isomer- 2Glc	U, F

a: Stands for [M+HCOO]⁻.

Table S3 The relative content of each compound in plasma.

No.	Compound Name	Relative Content (%)	Total Content (%)
In positive ion mode			
<i>Lignans</i>			
1	Gomisin D isomer	0.003	58.868
2	Schizandrol A	3.606	
3	Gomisin D	2.064	
4	Schizandrol A isomer	0.079	
5	Gomisin J	0	
6	Gomisin J isomer	0	
7	Tigloyl gomisin Q/Angeloyl gomisin	0.008	
8	Kadsuranin/isomer	0	
9	Kadsuranin/isomer	0.444	
10	Tigloyl gomisin Q/Angeloyl gomisin Q	0.055	
11	Gomisin J isomer	0	
12	Benzoyl isogomisin Q	0.006	
13	Tigloyl gomisin Q isomer/Angeloyl gomisin Q isomer	0.039	
14	(-) Gomisin K ₁	0	
15	(+) Gomisin K ₂	0	
16	Schisantherin B	1.985	
17	(-) Gomisin K ₁ isomer/(+) Gomisin K ₂ isomer	0	
18	Schisantherin A	5.987	
19	Schisantherin B isomer	5.811	
20	Schisanhenol	0	
21	Gomisin E	0	
22	Schisandrin A	1.719	
23	Gomisin N	0	
24	Schisandrin B	0.046	
25	Tanshindiol B/Tanshindiol C	0.006	
26	1,2,6,7,8,9-Hexahydro-1,6,6-trimethyl-3,11-dioxanaphth[2,1-e]azulene-10,12-dione/isomer	0.008	
27	1 β -Hydroxy cryptotanshinone	0.009	
28	1,2-Dihydro-1,6-dimethylfuro[3,2-c]naphth[2,1-e]oxepin-10,12-dione	0.011	
29	6,7,8,9-Tetrahydro-1,6,6-trimethylfuro[3,2-c]naphth[2,1-e]exepine-10,12-dione	0.033	
30	6,7,8,9-Tetrahydro-1,6,6-trimethylfuro[3,2-c]naphth[2,1-e]exepine-10,12-dione isomer	0.019	
31	1-Oxo cryptotanshinone	0.154	
32	Tanshinone II B	0.066	
33	Hydroxytanshinone II A/3 α -Hydroxy tanshinone II A	0.080	
M1	Schisandrin A	2.863	
M2	Schisandrin A loss of 2CH ₂ +demmethylation to carboxylic acid	0.029	
M3	Schisandrin A loss of CH ₂ +di-oxidation	0.327	
M4	Schisandrin B oxidation	1.980	

M5	Schisandrin A loss of CH ₂ +di-oxidation	0.276	
M6	Schisandrin B loss of CH ₂ +di-oxidation	0.055	
M7	Schisandrin A loss of 2CH ₂ +demethylation to carboxylic acid	5.156	
M8	Schisandrin B oxidation	0.176	
M9	Schisandrin A loss of CH ₂ +di-oxidation	0.032	
M10	Schisandrin B oxidation	0.859	
M11	Schisandrin A ethyl to carboxylic acid	2.420	
M12	Schisandrin B oxidation	0.690	
M13	Schisandrin A loss of OCH ₂ +carbonyl formation	0.457	
M14	Schisandrin A demethylation to carboxylic acid	0.142	
M15	Schisandrin A loss of OCH ₂ +carbonyl formation	0.300	
M16	Schisandrin A loss of CH ₂ +oxidation	0.262	
M17	Schisandrin A loss of 2CH ₂ +acetylation	4.718	
M18	Schisandrin A loss of OCH ₂ +carbonyl formation	1.983	
M19	Schisandrin A loss of CH ₂ +oxidation	0.540	
M20	Schisandrin A loss of OCH ₂ +carbonyl formation	0.549	
M21	Schisandrin A loss of CH ₂ +oxidation	0.451	
M22	Schisandrin A loss of OCH ₂ +ketone formation	0.207	
M23	Schisandrin A loss of OCH ₂ +ketone formation	0.109	
M24	Schisandrin B methylene to Ketone	0.031	
M25	Schisandrin A loss of OCH ₂ +bis-ketone formation	0.874	
M26	Schisandrin B methylene to Ketone	0.039	
M27	Schisandrin A loss of OCH ₂ and CH ₂ +acetylation	3.196	
M28	Schisandrin A loss of 2OCH ₂ +demethylation to carboxylic acid	0.055	
M29	Schisantherin B -OCH ₂	2.384	
M30	Schisandrin A loss of 2CH ₂	0.040	
M31	Schisandrin A loss of OCH ₂ and CH ₂ +acetylation	2.689	
M32	Schisandrin A loss of OCH ₂ +ketone formation	0.059	
M33	Schisandrin A loss of 2CH ₂ +acetylation	0.400	
M34	Schisandrin A loss of OCH ₂ +bis-ketone formation	0.393	
M35	Schisandrin A loss of OCH ₂ +bis-ketone formation	0.384	
M36	Schisandrin A loss of OCH ₂ +bis-ketone formation	0.797	
M37	Schisandrin A loss of CH ₂	0.710	
<i>Tanshinones</i>			
34	Tanshinone VI	1.872	40.326
35	1,2-Dihydro-tanshinquinone I /15,16-Dihydrotanshinone	0.099	
36	Danshenxinkun B	0.004	
37	Methyl tanshinonate	0.006	
38	Tanshinone I	10.453	
39	Cryptotanshinone	7.119	
40	Unknown	0.004	
41	Tanshinone II A	4.231	
M38	Tri-hydroxylation cryptotanshinone	2.598	

M39	Hydroxylation tanshinone I	0.400	
M40	Hydroxylation cryptotanshinone	3.617	
M41	Hydroxylation cryptotanshinone	0.172	
M42	Hydroxylation cryptotanshinone	0.249	
M43	Di-hydroxylation cryptotanshinone	0.153	
M44	Di-hydroxylation tanshinone IIA	7.123	
M45	Hydroxylation tanshinone I	0.725	
M46	Di-hydroxylation cryptotanshinone	0.090	
M47	Di-hydroxylation cryptotanshinone	0.522	
M48	Hydroxylation cryptotanshinone	0.098	
M49	Hydroxyl tanshinone IIB	0.433	
M50	Hydroxylation tanshinone II A	0.075	
M51	Di-hydroxylation cryptotanshinone	0.032	
M52	Dehydrogenation tanshinone II A	0.250	
<i>Flavonoids</i>			
113	Vitexin	0	0
114	Calycosin	0	
<i>Lactones</i>			
115	3-Butylidenephthalide	0.469	0.806
116	Senkyunolide B/C/E	0.337	
In negative ion mode			
<i>Ginsenosides</i>			
42	Unknown	0.012	99.159
43	Re ₃	0.020	
44	Unknown	0.037	
45	Re ₄	0.011	
46	20-Gluco-ginsenoside Rf	0.063	
47	Notoginsenoside R1 isomer	0.031	
48	Re ₁	0.049	
49	Notoginsenoside R ₁	0.052	
50	Re ₂	0.012	
51	Unknown	0.071	
52	Re	9.603	
53	Rg ₁	0.407	
54	Koryoginsenoside R ₂ isomer	0.201	
55	Floralginsenoside P/isomer	0.036	
56	Koryoginsenoside R ₂	0	
57	Koryoginsenoside R ₂ isomer	0	
58	Floralginsenoside P/isomer	0.090	
59	Ginsenoside F ₃ /Ginsenoside F ₅	0.030	
60	Floralginsenoside P/isomer	0.059	
61	Floralginsenoside P/isomer	0.021	
62	Notoginsenoside N isomer	0.468	

63	Notoginsenoside N	0.340
64	Vinaginsenoside R ₄	0.212
65	Unknown	0
66	Unknown	0
67	Rf isomer	0.048
68	Rf	2.719
69	Unknown	0
70	Notoginsenoside R ₂	0.096
71	Ra ₂	0.062
72	Ra ₃	0.239
73	Rb ₁	20.768
74	Ro isomer	0.069
75	Rg ₂	3.806
76	Ra ₁	0.082
77	Rc	11.740
78	20(R)-Rg ₂	0.552
79	Ro	0.818
80	Rh ₁	0.070
81	Ro isomer	0.635
82	Rb ₂	1.301
83	Rb ₃	0.807
84	Quinquenoside R ₁	0.133
85	Rb ₁ isomer	0
86	Pseudo-ginsenoside-RT ₁ /Chikusetsusaponin IV	0
87	Rs ₂	0.073
88	Rd	18.090
89	Malonyl-ginsenoside Rd	0
90	Quinquenoside R ₁ isomer	0
91	Acetyl-Rg ₂	0
92	Rd isomer	1.542
93	Acetyl-Rd/isomer	0
94	Ginsenoside Ro methyl ester	0.044
95	Gypenoside X VII	0
96	Vinaginsenoside R ₁₆	0.057
97	Pseudo-ginsenoside RC ₁	0
98	Gypenoside IX	0
99	Notoginsenoside Fe	0.116
100	Acetyl-gypenoside X VII	0
101	Acetyl-gypenoside X VII isomer	0
102	Pseudo-ginsenoside-RT1 isomer/Chikusetsusaponin IV isomer	0.743
103	Chikusetsusaponin IVa	6.131
104	Ginsenoside F ₂	0.638
105	Rg ₃	6.452

106	(20 <i>R</i>)-Rg ₃	2.062	
107	Acetyl-(<i>S/R</i>)-Rg ₃ /isomer	0	
108	Acetyl-(<i>S/R</i>)-Rg ₃ /isomer	0	
109	Polyacetyleneginsenoside-Ro/isomer	0	
110	Polyacetyleneginsenoside-Ro/isomer	0	
111	Rh ₂	0	
112	20(<i>R</i>)-Rh ₂	0	
M53	Monooxygenated Rb ₁	0.136	
M54	F ₁ /isomer	0.044	
M55	Ra ₃ -Xyl	2.688	
M56	Rd isomer	0.081	
M57	Rd isomer	0	
M58	F ₁ /isomer	0.108	
M59	Rd isomer	0	
M60	Ro-Glc	1.471	
M61	Ro-2Glc	2.913	
M62	Ro isomer-2Glc	0	
<i>Phenolicacids and triterpenoid acid</i>			
117	Salvianolic acid A	0	0
118	Salvianolic acid B	0	
119	Ursolic acid/Oleanlic acid	0	
<i>Astragalus saponins</i>			
120	Cyclocanthoside E	0	0.841
121	Astragaloside V/Astragaloside VI/Astragaloside VII	0	
122	Astragaloside IV	0.841	