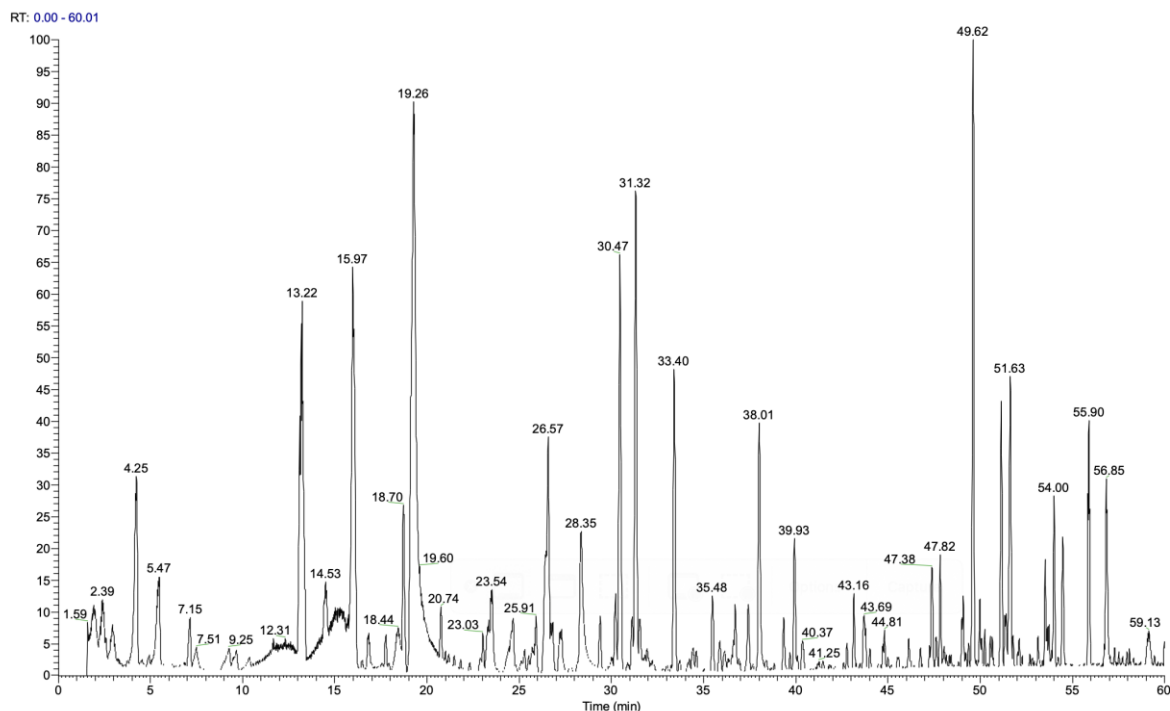
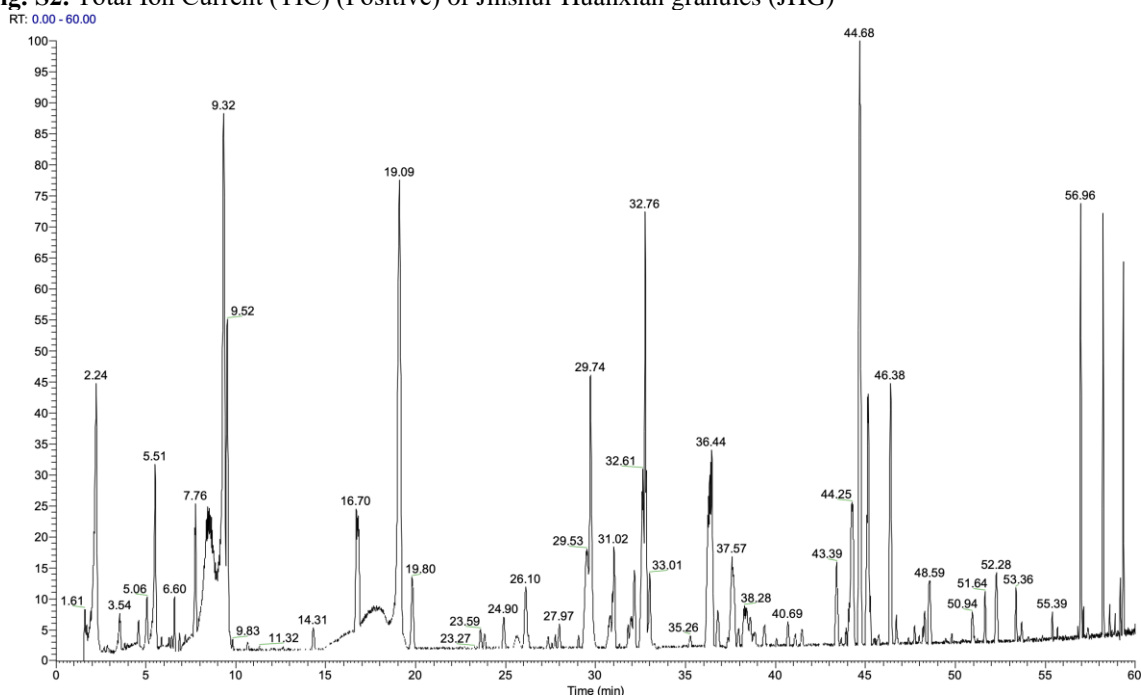


**Fig. S1.** Orbitrap Fusion MS of the 16 bioactive compounds for the specificity test (A: chromatogram of quality control sample B: chromatogram of sample C: chromatogram of blank plasma)



**Fig. S2.** Total Ion Current (TIC) (Positive) of Jinshui-Huanxian granules (JHG)



**Fig. S3.** Total Ion Current (TIC) (negative) of Jinshui-Huanxian granules (JHG)

**Table S1.** Main pharmacokinetic parameters of the control groups after intragastric administration of JHF. All data are presented as the mean  $\pm$  SD. ( $\bar{X} \pm S$ , n=6)

Compounds	C <sub>max</sub> (ng/mL)	AUC <sub>(0-t)</sub> (ng/mL·h)	AUC <sub>(0-∞)</sub> (ng/mL·h)	T <sub>max</sub> (h)	t <sub>1/2</sub> (h)	Clearances (L/h/kg)	MRT <sub>(0-t)</sub> (h)	MRT <sub>(0-∞)</sub> (h)	V <sub>ss</sub> (L)
Paeonol	6.6±1.48	42.41±8.94	55.56±12.98	0.75±0	13.23±1.77	96.12±25.03	7.84±0.03	16.14±1.86	1528.44±295.01
	11.68±2.03	48.6±10.06	59.21±14.79	0.75±0	11.12±1.41	160.75±36.26	6.91±0.23	12.71±1.67	2003.58±215.42
	15.72±1.66	105.8±6.95	130.64±20.95	2±0	9.02±3.68	141.44±23.61	7.77±0.37	13.34±3.52	1831.33±158.35
Nobiletin	2.51±0.77	15.57±4.99	21.14±6.95	0.75±0	13.49±1.64	16.29±3.64	8.63±0.2	17.79±2.23	287.56±59.62
	3.02±0.58	14.36±4.14	22.28±6.8	0.75±0	18.68±2.51	27.99±8.59	8.19±0.19	23.32±3.85	642.56±174.23
	4.46±1.06	17.94±4.56	25.92±9.57	0.75±0	16.19±7.02	48.34±15.08	7.37±0.43	19.53±7.12	882.05±234.11
Peimisine	1.49±0.16	12.45±2.56	19.5±5.73	4±0	16.51±2.09	0.15±0.04	9.16±0.22	22.84±3.24	3.26±0.57
	2.08±0.54	17.84±4.48	26.87±7.93	4±0	15.16±1.25	0.19±0.05	9.14±0.03	21.33±1.78	3.98±0.82
	2.35±0.53	34.92±8.14	48.89±9.74	8±0	11.37±0.71	0.2±0.03	11.34±0.11	19.75±0.92	3.96±0.82
Peiminine	2.91±0.9	29.08±8.48	31.89±9.55	4.67±1.15	6.06±0.22	2.77±0.84	8.01±0.09	10.17±0.32	28.03±8.27
	4.22±1.27	38.65±13.2	43.88±16.35	4±0	7.97±0.84	3.66±1.12	8.23±0.25	11.34±1.03	40.68±9.67
	5.31±1.61	41.98±11.72	46.14±13.69	3±0	6.82±0.57	6.72±1.81	7.84±0.1	10.12±0.42	67.52±15.96
Peimine	0.57±0.22	7.38±2.13	24.73±5.52	4±0	52.06±30.73	1.86±0.47	11.1±0.12	75.32±41.77	131.39±53.45
	1.49±0.26	14.58±1.9	17.65±2.24	3.33±0.58	8.02±0.39	4.53±0.57	8.8±0.32	13.46±0.58	61.2±9.95
	2.53±0.56	26.58±4.11	29.93±4.92	2.67±0.58	7.23±0.62	5.32±0.73	8.43±0.11	11.32±0.63	60.06±7.12
Cynaroside	43.95±5.61	290.14±24.36	312.14±25.99	6±0	5.75±0.55	0.06±0.01	7.83±0.02	9.56±0.13	0.6±0.08
	57.73±5.09	402±39.16	433.12±43.54	6±0	5.75±0.11	0.08±0.01	8.56±0.09	10.26±0.15	0.83±0.06
	79.54±3.5	438.04±27.59	471.52±31.33	6±0	5.1±0.13	0.15±0.01	7.51±0.01	9.2±0.11	1.35±0.09

Hesperidin	3.21±0.67	22.12±3.51	25.8±4.55	2±0	7.7±0.63	195.87±17.16	7.52±0.11	11.4±0.44	2228.19±131.09
	9.01±1.03	56.74±8.01	60.9±8.78	3±0	5.14±0.25	148.43±20.1	6.2±0.18	7.91±0.43	1170.37±124.18
	10.27±1.47	70.01±8.49	96.38±13.43	3±0	17.64±6.08	186.2±31.33	7.55±0.24	19.29±6.7	3498.95±860.43
Ginsenoside Rb <sub>1</sub>	8.54±0.92	92.72±6.92	140.14±22.61	5.33±1.15	14.83±4.95	5.5±1.16	9.74±0.53	21.93±6	115.88±11.46
	36.65±6.14	193.52±40.15	286.62±70.82	1.5±0	15.9±12.05	4.95±1.57	8.09±0.52	21.73±13.11	98.14±39.67
	73.68±6.13	516.19±26.29	624.04±99.95	1.5±0	9.1±4.28	4.34±0.71	7.71±0.52	12.85±4.23	53.81±7.92
Ginsenoside Rb <sub>2</sub>	18.54±2.52	105.98±15.54	126.15±24.65	0.5±0	8.5±0.48	5.69±1.15	7.25±1.01	11.7±2.17	64.99±2.67
	29.35±2.39	119.72±13.55	162.39±48.14	0.5±0	14.41±6.88	8.08±1.98	7.45±0.38	17.16±7.89	128.29±24.51
	48.52±5.05	175.37±25.35	220.83±43.54	0.5±0	11.5±1.62	11.47±2.05	7.12±0.36	13.89±2.08	156.49±6.77
Ginsenoside Rc	5.06±0.74	65.34±9.13	106.24±46.97	4.67±1.15	16.43±9.45	7.42±2.84	10.12±0.36	24.24±12.3	157.55±20.92
	13.36±1.28	125.93±11.87	135.62±15.56	3.33±0.58	5.79±0.58	9.33±1.27	7.68±0.27	9.42±0.82	87.15±5.34
	21.97±2.21	180.61±19.79	210.55±24.72	2.67±0.58	7.84±0.67	11.86±1.23	7.96±0.24	11.84±0.36	140.17±11.84
Icariin	3.48±0.65	16.03±2.39	27.34±9.45	0.083±0	21.46±8.07	38.71±11.38	8.53±0.57	27.35±10.67	978.36±136.13
	5.11±0.56	21.24±2.58	27.51±3.65	0.083±0	10.68±2.11	64.85±7.46	7.8±0.22	14.99±0.93	971.6±122.73
	7.68±1.54	26.41±6.87	37.12±9.77	0.083±0	12.26±2.42	98.06±22.27	8.33±0.4	17.95±0.96	1766.12±449.66
Catalpol	4.74±0.33	36±5	40.71±7.32	3.33±0.58	8.07±1.5	0.26±0.06	7.56±0.41	10.73±1.77	2.67±0.25
	7.28±1.13	47.29±6.22	53.74±6.51	1.5±	7.72±0.04	0.34±0.04	7.64±0.12	10.96±0.16	3.72±0.45
	9.2±0.59	34.64±3	51.06±7.12	0.92±0.14	17.32±4.81	0.71±0.11	7.64±0.29	20.98±4.11	14.68±2.04
Rutin	10.78±2.18	21.44±8.06	44.34±32.27	0.083±0	29.9±16.87	0.46±0.23	7.33±0.65	36.15±22.73	13.09±2.88
	14.72±1.48	27.94±5.14	34.53±7.86	0.083±0	12.12±0.95	0.83±0.16	5.85±0.43	12.48±1.51	10.15±0.94
	19.23±2.32	30.72±5.92	55.86±21.64	0.083±0	31.15±15.78	1.12±0.53	6.35±0.43	34.55±19.24	32.16±11.41

Apigenin-7-glucoside	1.99±0.17	20.23±1.99	29.09±6.32	1.83±0.2	15.36±4.12	0.2±0.04	8.84±0.05	20.09±4.89	3.94±0.41
	3.22±0.44	22.23±2.68	28.91±6.86	1.5±0	10.99±5.32	0.36±0.08	7.89±0.21	15.27±4.77	5.33±0.41
	3.88±0.42	36.55±5.3	46.51±7.55	1.67±0.29	9.62±0.54	0.44±0.07	8.8±0.07	15±0.61	6.6±0.86
Wedelolactone	18.55±3.98	109.53±24.74	139.11±45.63	2±0	10.72±3.69	0.003±0.001	7.52±0.34	14.01±3.66	0.04±0
	27.83±2.35	242.14±32.4	275.6±35.59	3.67±0.58	8.01±1.33	0.003±0	8.23±0.18	11.59±1.32	0.03±0.01
	35.4±2.29	220.65±17.2	262.29±13.51	1.83±0.29	8.2±0.63	0.006±0	7.5±0.21	12.01±1.32	0.07±0.01
Isoacteoside	5.67±1	32.21±4.75	35.79±5.5	1±0	6.86±0.48	0.91±0.18	7.15±0.14	9.81±0.84	8.97±2.22
	9.31±1.05	54.91±7.53	61.54±8.17	2±0	8.24±4.54	0.94±0.1	7.03±0.29	10.43±4.06	9.67±3.39
	18.44±1.98	96.4±18.12	104.4±22.39	3±0	6.1±0.77	1.12±0.23	6.64±0.33	8.58±0.98	9.42±1.03

**Table S2.** Main pharmacokinetic parameters of the PF model group after intragastric administration of JHF. All data are presented as the mean ± SD. (X̄±S, n=6)

Compounds	C <sub>max</sub> (ng/mL)	AUC <sub>(0-t)</sub> (ng/mL·h)	AUC <sub>(0-∞)</sub> (ng/mL·h)	T <sub>max</sub> (h)	t <sub>1/2</sub> (h)	Clearances (L/h/kg )	MRT <sub>(0-t)</sub> (h)	MRT <sub>(0-∞)</sub> (h)	V <sub>ss</sub> (L)
Paeonol	2.79±0.6*	21.82±2.86*	41.77±12.11	0.5±0	25.5±8.84	93.8±25.66	9.14±0.1**	33.81±11.44	2980.29±449.33*
	3.16±0.22**	24.54±2.15*	41.58±9.78	0.75±0	19.16±6.63	316.18±67.77*	9.7±0.37**	26.89±8.95	8115.77±895.52*
	3.63±0.33**	34.97±1.86**	83.36±34.32	3±0	36.4±25.65	282.84±90.76	9.41±0.4**	49.6±33.28	12017.41±3866.6*
Nobiletin	2.97±0.67	21.64±3.48	33.4±4.41	0.75±0	17.64±1.82*	7.16±0.71*	8.86±0.2	23.25±2.12*	166.86±26.65*
	3.37±0.53	20.03±2.62	43.11±11.09	0.75±0	31.46±13.26	19.65±5.02	9.13±0.25**	41.81±18.37	769.75±168.2
	3.57±0.3	15.48±2.99	17.96±3.39	0.75±0	9.59±3.39	78.42±15.85	6.66±0.35	11.05±1.44	864±195.9
Peimisine	2.05±0.49	12.31±2.23	14.62±2.48	1.5±0	7.2±0.28**	0.14±0.02	7.56±0.17**	11.83±0.51**	1.62±0.32*
	2.51±0.55	23.44±5.01	26.76±5.8	3.67±0.58	8.25±0.94**	0.26±0.05	7.92±0.2**	11.39±1.05**	2.91±0.52
	2.76±0.48	29.71±5.82	33.14±6.82	8±0	5.96±0.23**	0.35±0.06*	9.84±0.24**	12.17±0.39**	4.24±0.61

Peiminine	2.9±0.47	22.85±2.61	39.76±7.22	3±0	23.2±5.2**	1.54±0.23	8.41±0.09**	29.31±6.36**	44.32±5.6*
	6.1±1.14	46.56±8.45	53.38±10.3	2±0	6.9±0.28	3.94±0.72	7.7±0.15*	11.03±0.46	43.3±6.88
	7.52±1.33	45.99±7.27	60.7±7.68	2±0	13.32±1.69**	5.66±0.74	8.23±0.1**	16.82±1.78**	95.87±20.6
Peimine	0.58±0.28	6.96±3.07	10.76±3.94*	2±0	14.3±1.49	3.22±0.99	9.84±0.23**	22.57±2.38	74.22±28.56
	1.72±0.37	20.41±3.87	37.1±9.76*	2.33±0.58	21.76±6.99*	3.11±0.86	9.82±0.12**	30.39±8.97*	91.13±22.81
	2.19±0.54	16.76±3.5*	19.8±4.16	2±0	8.17±1.23	9.64±1.83*	7.82±0.18**	12.12±1.15	116.13±19.39**
Cynaroside	46.2±2.06	423.85±24.91**	476.73±29.92**	3±0	7.21±0.57*	0.03±0**	8.78±0.26**	11.62±0.81*	0.34±0.02**
	83.26±7.88**	560.68±41.87**	614.53±46.51**	6±0	5.37±0.13*	0.08±0.01	9.11±0.12**	11.09±0.19**	0.88±0.08
	134.6±8.44**	958.86±41.44**	1036.81±55.15**	6±0	5.13±0.72	0.08±0.01**	7.94±0.51	9.7±1.19	0.76±0.08**
Hesperidin	5.05±1.07	26.67±4.06	40.84±14.26	0.5±0	15.89±9.61	94.98±28.23**	8.25±0.12**	21.69±9.82	1878.92±191.23
	6.94±1.14	38.5±5.98*	48.11±7.84	0.58±0.14*	9.55±3.8	261.62±41.62*	7.56±0.32**	13.74±3.36*	3564.26±885.36*
	9.73±1.58	36.83±5.42**	53.46±11.2*	* 0.75±0	17.76±2.85	401.29±71.2**	7.59±0.12	20.55±3.29	8093.51±500.52*
Ginsenoside Rb1	8.58±1.21	64.71±8.4*	93.5±5.54*	2±0**	17.19±2.77	5.85±0.49	8.06±0.06**	20.8±3.1	122.64±27.46
	12.41±1.04**	132.19±16.63	177.59±32.82	3±0	11.71±1.42	10.76±2.16*	9.41±0.22*	17.35±2.14	183.67±15.59*
	29.18±2.09**	275.87±11.73**	451.38±35.94*	3±0	18.14±1.31*	7.01±0.44**	9.43±0.01**	25.24±1.65**	176.57±2.42**
Ginsenoside Rb2	7.13±0.66**	39.02±5.58**	44.68±9.34**	1.5±0	8.82±3.63	11.62±2.13*	6.35±0.23	10.16±2.62	114.37±8.23**
	10.68±0.81**	51.23±7**	63.18±8.7*	0.75±0	11.16±2.36	27.69±3**	7.54±0.02	13.77±2.04	380.31±62.68**
	13.53±1.31**	102.3±15.13*	113.4±19.38*	2±0	6.94±0.93*	26.4±5.05**	7.45±0.46	9.99±1.21*	259.84±18.48**
Ginsenoside Rc	9.7±0.81**	60.82±4.16	65.09±4.04	2.67±0.58	5.95±0.44	7.81±0.52	6.73±0.45**	8.42±1	65.52±5.84**
	7.45±1.72**	51.37±6.66**	59.74±9.14**	0.5±0**	8.98±0.81**	29.46±4.2**	7.97±0.54	11.98±1.19*	349.52±13.66**
	12.67±1.2**	117.75±15.87*	134.85±21.57*	6±0**	6.95±1.23	22.15±3.72*	8.95±0.43*	12.09±1.31	264.75±16.5**

<b>Icariin</b>	5.03±1.67	17.33±4.3	25.58±8.7	0.083±0	15.46±3.04	30.05±9.19	8.67±0.19	20.49±3.84	593.51±107.45*
	8.94±2.26*	25.98±7.94	39.82±18.43	0.083±0	18.58±8.45	70.43±30.22	7.64±0.44	22.18±9.82	1375.51±378.99
	33.76±2.43**	41.42±8	50.71±12.55	0.083±0	13.14±2.84	85.16±21.02	5.24±0.29**	12.01±2.57*	986.8±70.97*
<b>Catalpol</b>	2.41±0.19**	22.81±1.65*	26.81±2.42*	3±0	8.26±0.23	0.27±0.02	8.29±0.08*	12.38±0.36	3.39±0.17*
	2.93±0.39**	21.55±3.64**	28.67±7.59*	3±0	12.24±3.62	0.91±0.23	8.16±0.24*	16.31±3.81	14.32±0.95**
	4.92±0.5**	40.89±5.78	48.38±9.34	3±0**	9.37±1.69	0.89±0.13	7.78±0.24	12.3±1.88*	10.82±0.73*
<b>Rutin</b>	16.59±2.86*	28.48±5.62	46.79±20.43	0.083±0	23.27±10.82	0.27±0.02	6.89±0.47	26.14±13.74	6.07±1.1*
	25.8±3.39**	49.09±8.67*	71.34±23.58	0.083±0	16.2±5.74	0.91±0.23*	7.85±0.45**	19.85±7.03	10.63±1.35
	37.05±3.02**	66.33±19.05*	88.67±20.05	0.083±0	15.47±8.31	0.89±0.13	6.74±0.54	17.57±8.16**	13.32±6.2
<b>Apigenin-7-glucoside</b>	0.89±0.09**	10.33±2.48**	37±23.83	0.75±0**	51.09±30.25	0.15±0.1	10.28±0.35**	72.46±41.27	8.27±1.79*
	1.12±0.21**	10.37±2.06**	35.08±20.21	0.75±0	50.06±35.82	0.5±0.28	10.35±0.33**	71.08±50.33	28.13±6.93**
	1.29±0.19**	13.53±3.26**	35.78±10.37	1±0*	36.79±10.35*	0.71±0.19	10.46±0.19**	52±14.25*	35.51±8.06**
<b>Wedelolactone</b>	28.94±4.76*	123.16±20.76	147.59±26.83	0.75±0	9.87±3.09	0.002±0	7.09±0.38	12.32±3.09	0.03±0.01**
	33.45±4.8	208.21±30.44	239.66±37.23	1.5±0**	8.45±1.09	0.005±0.001*	7.17±0.05**	10.97±0.54	0.05±0.01*
	57.72±4.16**	292.92±30.82*	321.22±41.64	2±0	7.16±1.58	0.006±0.001	6.21±0.47*	8.62±1.19*	0.05±0*
<b>Isoacteoside</b>	5.09±0.84	51.74±8.76*	122.01±76.74	3.33±0.58*	35.69±34.63	0.24±0.12**	9.32±0.41**	48.85±47.3	8.18±3.1
	11.05±1.79	102.39±22.45*	129.24±35.86*	6±0	9.25±2.16	0.64±0.16	8.95±0.5**	14.71±2.44	9.2±1.33
	14.56±1.45	152.04±19.45*	165.86±24.94*	8±0	5.35±0.65	0.82±0.1	9.78±0.25**	11.57±0.81*	9.42±0.8

\* indicates p < 0.05 compared with the control group of the same dose, statistically difference;

\*\* indicates p < 0.01, statistically high difference