

**He-Wei granules (HWKL) combat cisplatin-induced nephrotoxicity
and myelosuppression in rats by inhibiting oxidative stress,
inflammatory cytokines and apoptosis**

Zehai Song¹, Hang Chang¹, Na Han¹, Hao Gao¹, Jingxuan Shao¹, Zhonglin Wang¹,
Zhihui Liu¹, Ye Liu², Hui Wang², Jun Yin^{1*}

¹Development and Utilization Key Laboratory of Northeast Plant Materials, School of
Traditional Chinese Materia Medica, Shenyang Pharmaceutical University, Shenyang
110016, China.

²Beijing Handian Pharmaceutical Co., Ltd, Beijing 100020, China.

* Corresponding author

Prof. Jun Yin

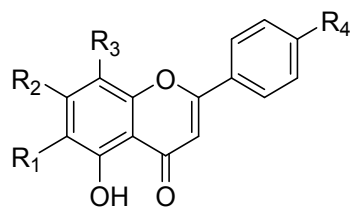
School of Traditional Chinese Materia Medica 48[#], Shenyang Pharmaceutical
University, Wenhua Road 103, Shenhe District, Shenyang 110016, China

TEL Numb: +86-24-2398-6491

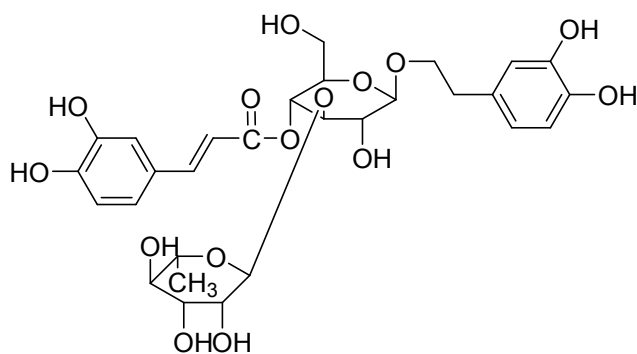
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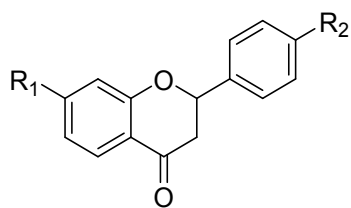
Supplementary Fig. S1 The chemical structures of 37 constituents identified in the HWKL extract



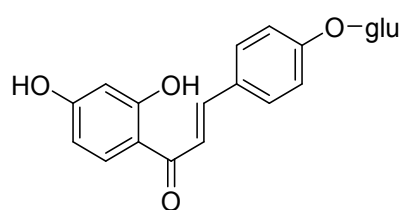
Compound	R ₁	R ₂	R ₃	R ₄
Scutellarin (7)	OH	O-glucuronyl	H	OH
Isomer of Chrysin-6-C- Arabinoside-8-C- Glucoside (8)	C-arabinosyl	OH	C-glucosyl	H
Chrysin-6-C- Arabinoside-8-C- Glucoside (9)	C-glucosyl	OH	C-arabinosyl	H
Baicalin (16)	OH	O-glucuronyl	H	H
Isomer of baicalin (17)	H	O-glucuronyl	OH	H
Wogonoside (21)	H	O-glucuronyl	OCH ₃	H
Oroxylin A 7-O- glucuronide (22)	OCH ₃	O-glucuronyl	H	H
Wogonin (36)	H	OH	OCH ₃	H



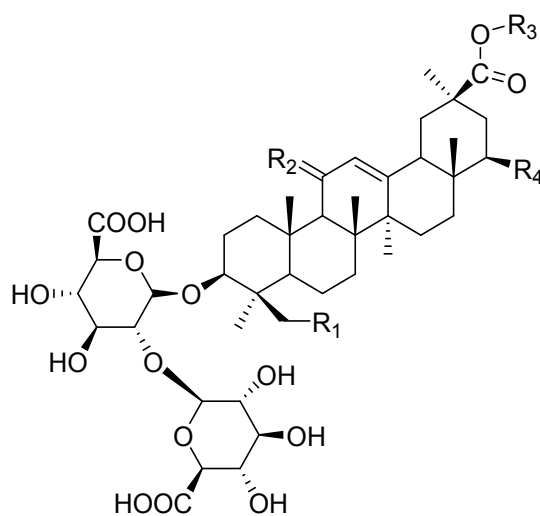
acteoside (10)



Compound	R ₁	R ₂
Liquiritigenin 7-O-Glucoside-4'-O-Apiosyl-O-glucoside (3)	O-glucosyl	O-Apiosyl-O-glucosyl
Liquiritin (4)	OH	O-glucosyl

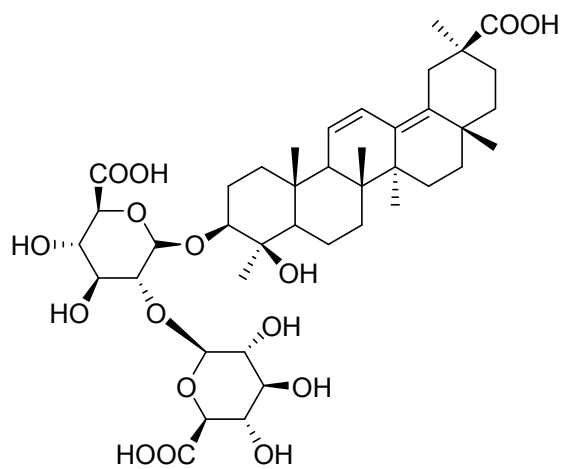


isoliquiritin (5)

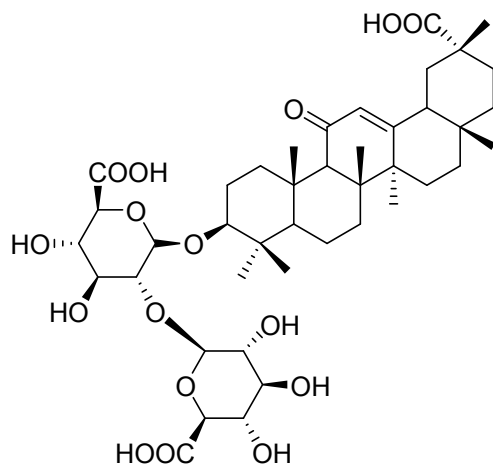


Compound	R ₁	R ₂	R ₃	R ₄
22-β-Acetoxy licorice saponin G2 (23)	OH	O	H	—O—C(=O)—CH_3
22-β- Acetoxyglycyrrhizic acid (24)	H	O	H	—O—C(=O)—CH_3
Licorice saponin G2 (31)	OH	O	H	H

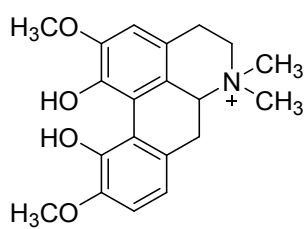
Licorice saponin J2 (33)	OH	2H	H	H
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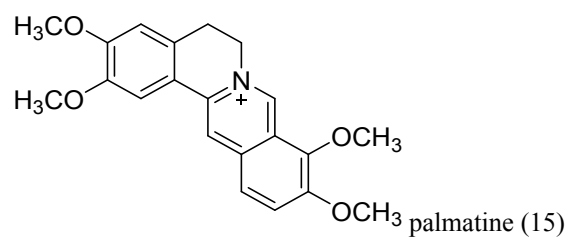
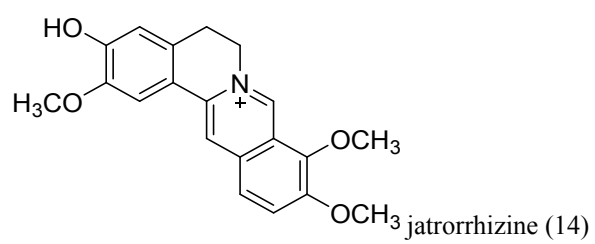
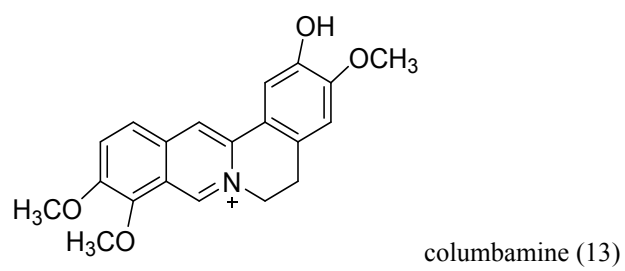
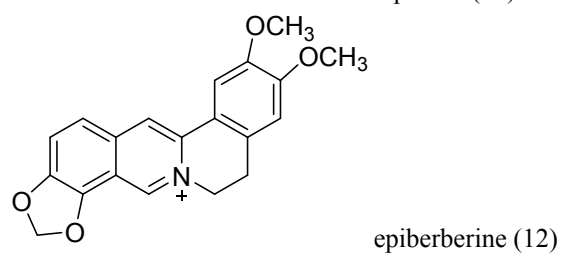
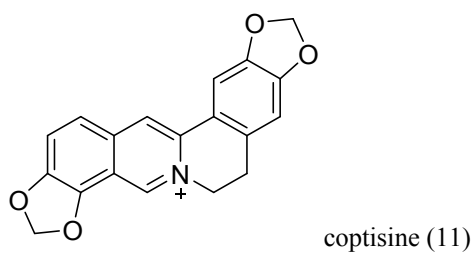
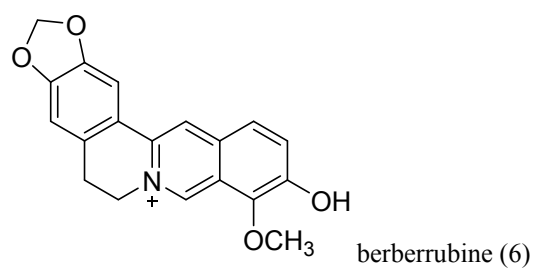
Licorice saponin K2 (34)

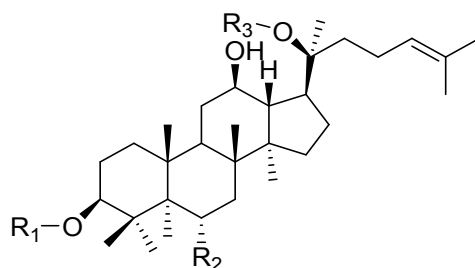
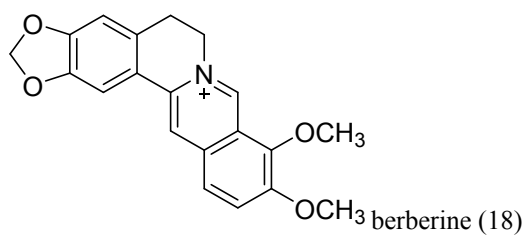


Licorice saponin H2 (32)

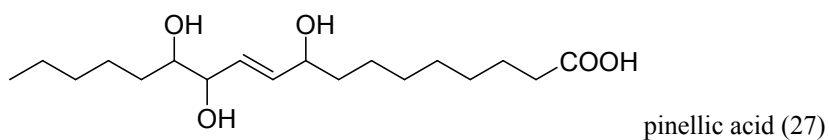
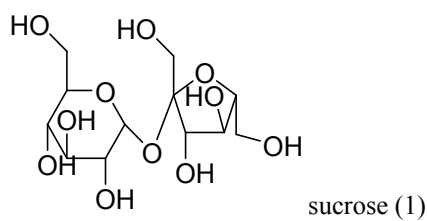
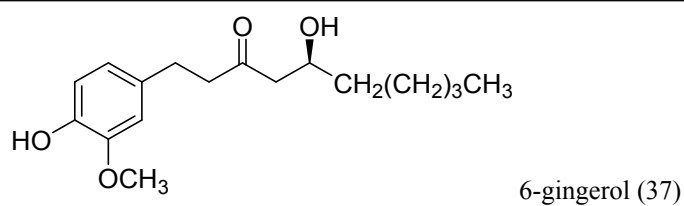


magnoflorine (2)





Compound	R ₁	R ₂	R ₃
ginsenoside Rg1 (19)	H	O-Glu	Glu
ginsenoside Re (20)	H	O-Glu (2→1) Rha	Glu
20S-ginsenosideRg2/20R-ginsenosideRg2 (25)	H	O-Glu (2→1) Rha	H
ginsenoside Rb1 (26)	Glu (1→2) Glu	H	Glu (6→1) Glu
ginsenoside Rc (28)	Glu (1→2) Glu	H	Glu (6→1) Ara (fu)
ginsenoside Rb2 (29)	Glu (1→2) Glu	H	Glu (6→1) Ara (py)
ginsenoside Rb3 (30)	Glu (1→2) Glu	H	Glu (6→1) Xyl
ginsenoside Rd (35)	Glu (1→2) Glu	H	Glu



Supplementary Table S1 The identified phytochemical compound and their properties and concentrations in HWKL extract detected by UHPLC-Q-TOF-MS/MS

No.	Identification	t _R (min)	Formula	[M-H]-			[M+HCOO]-			[M+H]+			Fragment ions (MS ²)	Source	Contents (Mean ± SEM; mg/g)
				detected	expected	Error (ppm)	detected	expected	Error (ppm)	detected	expected	Error (ppm)			
1	sucrose	0.402	C ₁₂ H ₂₂ O ₁₁	329.2306	329.2305	0.30							387.1466	*	350.06 ± 11.0*
2	magnoflorine	4.802	C ₂₀ H ₂₄ NO ₄ ⁺							342.1705	342.1692	3.79	342.1682,297.1106,282.0868, 265.0845,237.0884	CR	
3	Liquiritigenin 7-O- Glucoside-4'-O- Apiosyl-O-glucoside	5.027	C ₃₂ H ₄₀ O ₁₈	711.2137	711.2139	-0.28							711.2139,549.1936, 255.0644,135.0078	GHR	
4	Liquiritin	6.179	C ₂₁ H ₂₂ O ₉	417.1186	417.1189	-0.71							255.0655,135.0083,119.0499	GHR	21.56 ± 0.69
5	Isoliquiritin	6.298	C ₂₁ H ₂₂ O ₁₀	417.1186	417.1187	-0.23							417.1183,255.0656	GHR	32.88 ± 5.18
6	berberrubine	6.352	C ₁₉ H ₁₆ NO ₄ ⁺							322.1079	322.1082	-0.93	322.1082,307.0846,279.0894	CR	
7	Scutellarin	6.497	C ₂₁ H ₁₈ O ₁₂	461.0720	461.0726	-1.30							285.0399	SR	10.01 ± 0.56
8	Isomer of Chrysin-6- C-Arabinoside-8-C- Glucoside	6.576	C ₂₆ H ₂₈ O ₁₃	547.1452	547.1447	0.91							367.0805,337.0702,309.0778, 271.0788	SR	
9	Chrysin-6-C- Arabinoside-8-C- Glucoside	6.815	C ₂₆ H ₂₈ O ₁₄	547.1452	547.1451	0.18							547.1451,457.1171,427.1074, 367.0825,337.0714	SR	
10	Acteoside	6.934	C ₂₀ H ₃₆ O ₁₅	623.1996	623.198	2.56							623.1955,461.1673,161.0243	SR	
11	coptisine	6.988	C ₁₉ H ₁₄ NO ₄ ⁺							320.0903	320.0899	1.25	320.0892,292.0948,262.0842, 249.0759	CR	
12	epiberberine	6.988	C ₂₀ H ₁₈ NO ₄ ⁺							336.1216	336.1215	0.30	320.0894,292.0950	CR	

13	columbamine	7.036	C ₂₀ H ₂₀ O ₄ N ⁺					338.1392	338.1389	0.88	323.1129,308.0890,294.1197, 280.0966	CR	
14	jatrorrhizine	7.275	C ₂₀ H ₂₀ O ₄ N ⁺					338.1392	338.1394	-0.59	338.1389,323.1149,308.0926, 294.1120	CR	
15	palmatine	7.394	C ₂₁ H ₂₂ O ₄ N ⁺					352.1539	352.1533	1.70	337.1293,322.1065,308.1266, 294.1098	CR	
16	baicalin	7.768	C ₂₁ H ₁₈ O ₁₁	445.0771	445.0778	-1.57					891.1613,445.0774,269.0451, 175.0244	SR	17.85 ± 1.82
17	isomer of baicalin	7.808	C ₂₁ H ₁₈ O ₁₁	445.0771	445.0773	-0.44					445.0769,269.0443	SR	
18	berberine	7.87	C ₂₀ H ₁₈ NO ₄ ⁺					336.1236	336.124	-1.19	336.1226,321.0982,320.0920, 306.0756,292.0962,278.0799	CR	2.95 ± 0.31
19	ginsenoside Rg1	7.967	C ₄₇ H ₇₂ O ₁₄				845.4904	845.4899	0.59		845.4877,799.4812,637.4286	GR	0.90 ± 0.11
20	ginsenoside Re	7.967	C ₄₈ H ₈₂ O ₁₈				991.5483	991.547	1.31		637.4276,475.3780	GR	0.28 ± 0.02
21	wogonoside	8.484	C ₂₂ H ₂₀ O ₁₁	459.0928	459.0929	-0.21					283.0606,268.0372	SR	
22	Oroxylin A 7-O-glucuronide	8.722	C ₂₂ H ₂₀ O ₁₁	459.0928	459.0926	0.43					283.0607,268.0358	SR	
23	22-β-Acetoxylicorice saponin G2	8.961	C ₄₄ H ₆₄ O ₁₉	895.3964	895.3964	0					895.3907,351.0563	GHR	
24	22-β-Acetoxyglycyrrhizic acid	9.517	C ₄₄ H ₆₄ O ₁₈	879.3015	879.3025	-1.13					901.3726,879.3876,351.0537, 193.0329	GHR	
25	20S-ginsenosideRg2/20R-ginsenosideRg2	9.914	C ₄₂ H ₇₂ O ₁₃				829.4955	829.496	-0.60		783.475	GR	
26	ginsenoside Rb1	9.994	C ₅₄ H ₉₂ O ₂₃				1153.6011	1153.6013	-0.17		1107.5921,945.5463	GR	0.72 ± 0.03

27	pinellic acid	10.034	C ₁₈ H ₃₃ O ₅						329.2312	PR	
28	ginsenoside Rc	10.153	C ₅₃ H ₉₀ O ₂₂		1123.5906	1123.591	-0.35		1077.5853,945.5407,783.4926,	GR	
									621.4333		
29	ginsenoside Rb2	10.351	C ₅₃ H ₉₀ O ₂₂		1123.5906	1123.5911	-0.44		1077.5802,783.4815	GR	
30	ginsenoside Rb3	10.391	C ₅₃ H ₉₀ O ₂₂		1123.5906	1123.5908	-0.17		1077.5844	GR	
31	Licorice saponin G2	10.55	C ₄₂ H ₆₂ O ₁₇	937.3909	937.393	-2.24			837.3930,351.0581,193.0326	GHR	
32	licorice saponin H2	10.59	C ₄₂ H ₆₂ O ₁₆	821.396	821.3962	-0.24			821.4043	GHR	
33	licorice saponin J2	10.63	C ₄₂ H ₆₄ O ₁₆	823.4016	823.4014	0.24			351.0561,193.0331	GHR	
34	licorice saponin K2	10.63	C ₄₂ H ₆₂ O ₁₇	821.396	821.3961	-0.12			821.3943	GHR	
35	ginsenoside Rd	10.749	C ₄₈ H ₈₂ O ₁₈		991.5483	991.548	0.30		945.5433,783.4934,621.4218	GR	
36	Wogonin	10.868	C ₁₆ H ₁₂ O ₅	283.0607	283.0607	0		0.59	283.0607,268.0358	SR	3.12 ± 0.45
37	6-gingerol	11.424	C ₁₇ H ₂₆ O ₄			6.37		1.31	257.0930,257.6282	ZB	0.17 ± 0.05

PR:Pinelliae Rhizoma Praeparatum (Araceae), ZB:Zingiberis Rhizoma Recens (Zingiberaceae), GR:Ginseng Radix Et Rhizoma (Araliaceae), SR:Scutellariae Radix (Labiateae), CR:Coptidis Rhizoma (Ranunculaceae), GHR:Glycyrrhizae Radix Et Rhizoma Praeparata Cum Melle (Leguminosae), JF:Jujubae Fructus (Rhamnaceae)

*content of sucrose was measured as the total amount of polysaccharide

* Polysaccharide are existed in all seven herbs so the source cannot be confirmed

Supplementary Table S2 Effect of HWKL on food consumptions at different time periods in cisplatin-treated rats ($\bar{X} \pm \text{SEM}$, g)

	blank	cisplatin	cisplatin + ondansetro n	cisplatin + domperido ne	cisplatin + BXXXT	cisplatin + hwkl low dose	cisplatin + hwkl middle dose	cisplatin + hwkl high dose	hwkl
dose		7.0 mg/kg	1.3 mg/kg	3.0 mg/kg	1.38 g/kg	1.18 g/kg	2.36 g/kg	4.725 g/kg	2.36 g/kg
-72h	29.35 ± 1.39	27.72 ± 1.46	30.33 ± 0.63	28.06 ± 1.89	29.50 ± 0.97	28.49 ± 1.02	27.94 ± 1.39	25.36 ± 1.46	27.52 ± 1.29
-48h	30.64 ± 1.22	26.41 ± 1.90	29.48 ± 1.12	28.75 ± 1.90	29.52 ± 1.65	31.06 ± 2.41	31.25 ± 1.30	29.21 ± 2.56	36.27 ± 1.04
-24h	29.63 ± 0.79	26.05 ± 1.33	31.91 ± 0.99	27.39 ± 0.99	31.18 ± 1.03	30.28 ± 1.64	28.78 ± 1.22	25.85 ± 1.72	31.04 ± 0.90
0h	28.26 ± 1.81	26.96 ± 1.13	29.11 ± 1.71	26.30 ± 1.21	29.43 ± 1.16	27.83 ± 1.31	28.15 ± 1.21	27.06 ± 0.98	30.30 ± 1.31
24h	27.08 ± 0.91	4.89 ± 0.41####	11.07 ± 0.80	6.85 ± 0.56	13.00 ± 0.53**	14.85 ± 0.68****	16.71 ± 1.53****	19.46 ± 1.08****	27.81 ± 0.95
48h	28.67 ± 1.18	2.86 ± 0.24####	7.99 ± 0.48	4.14 ± 0.37	6.48 ± 0.99	10.22 ± 0.23*	15.51 ± 1.54****	16.45 ± 1.94****	29.34 ± 0.90
72h	32.02 ± 1.07	0.06 ± 0.01####	5.42 ± 0.47	0.41 ± 0.07	6.36 ± 0.89	12.22 ± 0.95****	15.53 ± 1.15****	17.56 ± 3.07****	31.98 ± 1.15
96h	35.14 ± 1.05	6.19 ± 0.56####	6.77 ± 0.91	5.66 ± 0.39	14.32 ± 1.04*	14.76 ± 1.43****	17.01 ± 0.36****	18.55 ± 0.45****	33.27 ± 1.41
120h	36.13 ± 1.04	2.31 ± 0.32####	2.15 ± 0.62	3.37 ± 0.47	9.58 ± 0.78**	14.38 ± 1.49****	16.92 ± 1.89****	19.78 ± 2.75****	34.09

									± 1.36
144h	34.18 ± 1.47	6.72 ± 0.76####	11.83 ± 0.64	7.45 ± 0.66	14.60 ± 0.66**	16.08 ± 1.28***	18.33 ± 1.19****	23.16 ± 0.93****	33.41 ± 1.73
168h	34.40 ± 0.83	6.80 ± 0.75####	12.05 ± 0.23	8.77 ± 0.45	14.95 ± 1.36**	17.99 ± 1.35****	21.46 ± 1.95****	23.80 ± 1.29****	33.00 ± 1.05

Values were represented as Mean ± SEM. # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$, #### $p < 0.0001$, compared with the blank group, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, compared with the control group

Supplementary Table S3 Effect of HWKL on water consumptions at different time periods in cisplatin-treated rats ($\bar{X} \pm \text{SEM}$, g)

	blank	cisplatin	cisplatin + ondansetron	cisplatin + domperidone	cisplatin + BXXXT	cisplatin + hwkl low dose	cisplatin + hwkl middle dose	cisplatin + hwkl high dose	hwkl
dose		7.0 mg/kg	1.3 mg/kg	3.0 mg/kg	1.38 g/kg	1.18 g/kg	2.36 g/kg	4.725 g/kg	2.36 g/kg
-72h	58.68 $\pm$ 3.66	66.68 $\pm$ 2.78	60.68 $\pm$ 1.41	54.22 $\pm$ 3.07	66.47 $\pm$ 6.10	66.30 $\pm$ 3.47	68.82 $\pm$ 6.35	59.62 $\pm$ 1.60	67.77 $\pm$ 2.26
-48h	56.23 $\pm$ 2.59	61.33 $\pm$ 1.93	61.30 $\pm$ 4.35	62.68 $\pm$ 2.85	52.78 $\pm$ 4.09	55.42 $\pm$ 4.85	50.47 $\pm$ 4.14	54.05 $\pm$ 5.26	58.47 $\pm$ 1.43
-24h	51.08 $\pm$ 3.39	63.87 $\pm$ 1.48	57.02 $\pm$ 2.41	51.54 $\pm$ 3.72	62.90 $\pm$ 6.03	61.75 $\pm$ 3.70	54.88 $\pm$ 6.99	57.88 $\pm$ 6.99	56.23 $\pm$ 2.88
0h	58.70 $\pm$ 3.60	65.67 $\pm$ 2.14	63.55 $\pm$ 3.39	64.95 $\pm$ 2.50	59.85 $\pm$ 6.12	58.27 $\pm$ 4.38	56.35 $\pm$ 3.57	57.58 $\pm$ 5.49	58.43 $\pm$ 1.21
24h	52.93 $\pm$ 3.58	25.23 $\pm$ 2.04####	29.22 $\pm$ 1.84###	24.06 $\pm$ 1.04####	33.55 $\pm$ 3.68#	40.53 $\pm$ 2.93	42.34 $\pm$ 5.76	41.82 $\pm$ 2.80	55.30 $\pm$ 2.97
48h	49.60 $\pm$ 2.46	18.72 $\pm$ 1.23####	18.38 $\pm$ 1.98####	14.35 $\pm$ 0.82####	29.18 $\pm$ 1.10##	30.70 $\pm$ 2.54#	35.80 $\pm$ 1.38	36.87 $\pm$ 2.04	51.70 $\pm$ 1.97
72h	51.78 $\pm$ 2.06	14.83 $\pm$ 1.08####	22.02 $\pm$ 0.64####	13.08 $\pm$ 0.93####	27.80 $\pm$ 1.89####	33.30 $\pm$ 1.77#	37.95 $\pm$ 2.76	38.73 $\pm$ 1.95	54.90 $\pm$ 2.66
96h	52.70 $\pm$ 1.70	16.82 $\pm$ 0.55####	24.32 $\pm$ 5.03###	18.22 $\pm$ 1.70####	35.77 $\pm$ 2.40	43.82 $\pm$ 1.14	45.83 $\pm$ 1.27	43.13 $\pm$ 2.08	52.92 $\pm$ 2.22

120h	55.50 ± 2.28	31.15 ± 2.21 ^{####}	32.02 ± 1.87 ^{###}	28.90 ± 2.15 ^{####}	44.95 ± 2.34	52.00 ± 2.68	54.83 ± 1.56	55.28 ± 1.15	54.12 ± 3.77
144h	60.68 ± 1.85	39.72 ± 2.45 ^{##}	37.77 ± 1.69 ^{###}	32.94 ± 0.50 ^{####}	43.22 ± 2.69	50.95 ± 1.27	53.10 ± 2.63	54.72 ± 1.78	55.72 ± 1.87
168h	56.08 ± 2.39	35.65 ± 1.29 ^{##}	44.53 ± 1.66	38.02 ± 2.41	44.42 ± 2.50	51.45 ± 1.85	53.70 ± 2.20	56.73 ± 2.84	54.52 ± 3.40

Values were represented as Mean ± SEM. [#]*p*<0.05, ^{##}*p*<0.01, ^{###}*p*<0.001, ^{####}*p*<0.0001, compared with the blank group

Supplementary Table S4 Effect of HWKL on body weight at different time periods in cisplatin-treated rats ($\bar{x} \pm \text{SEM}$, g)

	blank	cisplatin	cisplatin + ondansetro n	cisplatin + domperidon e	cisplatin + BXXXT	cisplatin + hwkl low dose	cisplatin + hwkl middle dose	cisplatin + hwkl high dose	hwkl
dose		7.0 mg/kg	1.3 mg/kg	3.0 mg/kg	1.38 g/kg	1.18 g/kg	2.36 g/kg	4.725 g/kg	2.36 g/kg
-72h	310.92 ± 6.89	312.28 ± 8.62	308.82 ± 9.86	312.90 ± 5.35	313.27 ± 7.78	312.68 ± 7.63	313.10 ± 7.87	314.28 ± 6.20	312.70 ± 4.54
-48h	330.17 ± 7.84	328.87 ± 12.45	328.50 ± 10.07	328.28 ± 4.66	333.90 ± 8.02	329.77 ± 7.93	329.25 ± 5.05	334.63 ± 9.15	327.12 ± 5.82
-24h	334.27 ± 7.30	337.35 ± 12.97	336.17 ± 10.73	335.12 ± 4.26	339.93 ± 8.58	340.75 ± 7.56	341.33 ± 3.35	338.35 ± 9.05	334.08 ± 5.51
0h	350.28 ± 7.08	351.98 ± 12.03	354.13 ± 11.10	350.66 ± 5.32	350.12 ± 8.12	350.75 ± 11.06	351.80 ± 4.14	351.78 ± 11.37	352.33 ± 3.99
24h	365.00 ± 6.61	340.50 ± 13.14	340.28 ± 10.52	336.76 ± 7.68	328.57 ± 9.90	345.95 ± 9.79	359.53 ± 12.29	373.97 ± 4.37	365.33 ± 7.16
48h	372.05 ± 6.56	323.75 ± 6.33 [#]	320.08 ± 6.95 [#]	320.16 ± 6.94 [#]	329.72 ± 7.42	343.60 ± 7.17	365.68 ± 6.69	383.22 ± 3.11□□***	373.07 ± 7.22
72h	373.95 ± 6.68	312.37 ± 5.43###	313.53 ± 7.45###	303.60 ± 8.03####	336.37 ± 7.78	343.90 ± 8.84	366.63 ± 8.03**	376.92 ± 5.41****	381.13 ± 8.72
96h	372.95 ± 6.54	301.98 ± 5.53####	308.77 ± 7.53####	291.78 ± 9.11####	332.00 ± 8.29	332.62 ± 6.67	353.92 ± 5.34*	363.80 ± 6.97	384.68 ± 8.91
120h	381.60 ± 6.01	304.12 ± 6.34####	302.13 ± 9.46####	285.94 ± 7.36####	331.12 ± 7.07 [#]	330.98 ± 8.34 [#]	352.67 ± 7.51*	360.37 ± 8.20*	380.88 ± 9.02

144h	386.42 ± 5.78	303.75 ± 6.55####	303.82 ± 5.91####	285.50 ± 7.42####	332.57 ± 6.58##	334.17 ± 7.28 [#]	358.35 ± 8.27**	362.63 ± 8.33***	385.18 ± 9.28
168h	386.43 ± 5.56	295.93 ± 9.26####	299.22 ± 8.82####	280.03 ± 6.28####	330.48 ± 6.99##	334.38 ± 6.66 [#]	359.22 ± 4.34****	362.77 ± 7.55****	387.12 ± 8.96

Values were represented as Mean ± SEM. [#]*p*<0.05, ^{##}*p*<0.01, ^{###}*p*<0.001, ^{####}*p*<0.0001, compared with the blank group, **p*<0.05, ***p*<0.01, ****p*<0.001, *****p*<0.0001, compared with the control group, □□*p*<0.01, compared with the cisplatin + BXXXXT group