Supporting Information

Integrated analysis of phytochemical composition, pharmacokinetics and network pharmacology to probe the distinctions between the stems of *Cistanche deserticola* and *C. tubulosa* based on antidepressant activity

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Methods

Relative contents of glycosides and carbohydrates in Cistanche deserticola and C. tubulosa aqueous extracts

Cistanche deserticola aqueous extract (CDE) *and C. tubulosa* aqueous extract (CTE) were slowly stirred with ethanol (1:4, v/v) and placed at 4℃ for 24 h, respectively. Then, the precipitate and supernatant were collected by centrifugation at 4000 r/min for 20 min. The relative contents of total polysaccharides in CTE and CDE were determined from the collected precipitate by phenol-sulfuric acid colorimetric method with glucose as the standard. The remaining supernatant was then chromatographed over a D101 microporous resin column and eluted with distilled water. The relative contents of total oligosaccharides in CTE and CDE were determined from the collected eluents by phenol-sulfuric acid colorimetric method with glucose as the standard. And the relative contents of total glycosides in CTE and CDE were determined by UV–Vis spectrophotometry at 330 nm using echinacoside as the standard.

Chemical analysis by UPLC–QTOF–MS/MS analysis

The chromatographic separation was performed on an Agilent 1290 UPLC system (Agilent Ltd., USA) with an Agilent

ZORBAX Eclipse Plus C_{18} column (100 mm×2.1 mm i.d., 1.8 μm, Agilent Ltd., USA). The mobile phase consisted of 0.1% formic acid–water (v/v, mobile phase A) and 0.1% formic acid–acetonitrile (v/v, mobile phase B), and the gradient elution program at flow rate of 0.4 mL/min was as follows: mobile phase A at 95%A (0–4.00 min), from 95% to 80% (4.00–14.00 min), from 80% to 60% (14.00–17.00 min), from 60% to 5% (17–19 min) and maintaining at 5% (19.00–20.50 min). The temperature of column and autosampler was controlled at 35 °C and 4 °C, respectively. The injection volume was 5 μL. An Agilent G6545 QTOF mass spectrometer (Agilent Ltd., USA) equipped with electro spray ionization (ESI) source was operated in negative ionization mode. The mass spectrometer parameters were as follows: Gas Temp, 320 ℃; Gas Flow, 8L/min; nebulizer, 35 psig; Sheath Gas Temp, 350 ℃; Sheath Gas Flow, 11 L/min; VCap, 3500 V; Nozzle Voltage, 1000 V; Fragmentor, 175 V; Skimmer, 65 V; OCT1 RF Vpp, 750 V. Auto MS/MS mode was used to collect the data.

Chemical analysis by UPLC-QTRAP-MS/MS analysis

The analysis was performed in a SHIMADZU LC–20A UFLC system with an Applied Biosystem 5500 QTRAP hybrid triple-quadrupole mass spectrometer (Applied Biosystems/MDS Sciex, CA, USA), equipped with a turbo ion spray source. Chromatographic separation was performed on a ZORBAX Eclipse Plus C_{18} column (100 mm × 2.1 mm, 1.8 μm). The mobile phase consisted of 0.1% formic acid–water (v/v, mobile phase A) and 0.1% formic acid–acetonitrile (v/v, mobile phase B) and the gradient elution program at flow rate of 0.4 mL/min was as follows: mobile phase A at 95%~90% A (0–2.00 min), from 90% to 60% (2.00–7.00 min), from 60% to 5% (7.00–9.00 min), and maintaining at 5% (9.00–10.50 min). The column temperature and injection volume were set at 40℃ and 1 μL, respectively. An MS system operating in the negative electrospray ionization mode was employed in this study. Quantification was performed a multiple reaction monitoring (MRM) model of the transition and the parameters were as follows: TIS temperature, 550 °C; ionspray voltage, -4500 V; curtain gas, 25 $L \cdot min^{-1}$; Gas 1, 50 $L \cdot min^{-1}$; Gas 2, 50 $L \cdot min^{-1}$. The quantitative ion pairs of the measured compounds and corresponding DP and CE values are shown in Table S1. The sample data were collected and processed by Analyst 1.6.1 software (AB SCIEX, Concord, Canada). The method was validated for selectivity, linearity, lower limit of quantification, accuracy, precision, extraction recovery, matrix effect and stability according to the US Food and Drug Administration Bio-analytical Method Validation Guide.

Table S1 Mass spectrometry information of the measured compounds

Compounds	MRM（Da）	DP（eV）	CE（eV）
Echinacoside	785.3>623.0	–41	–51
Geniposide acid	373.2>211.1	–72	–14
8-Epiloganic acid	375.3>213.1	–130	–22
Verbascoside	623.4>160.9	–46	–39
Isoverbascoside	623.4>461.4	–40	–40
2’-Acetylverbsacoside	665.2>623.7.	–74	–40
Campneoside II	639.2>621.2	–40	–30
Tubuloside B	665.3>461.3	–50	–45
Cistanoside A	799.2>623.0	–50	–47
caffeic acid	179.0>117.0	–55	–34
3,4-dihydroxyphenyl-propionic acid	181.1>109.0	–50	–20
3-hydroxyphenylpropionic acid	165.1>106.0	–48	–32
hydroxytyrosol	153.2>122.1	–46	–30

Western blot analysis

The total protein from the PC12 cells and hippocampus were extracted and determined by BCA method. Equal amount of protein was separated on SDS-PAGE (10 mL 10% separation gel containing 2.7 mL H2O, 3.3 mL 30% Acr-Bis, 3.8mL 1M Tris-HCl (pH 8.8), 0.1 mL 10% SDS, 0.1 mL 10% ammonium persulfate, and 0.004 mL tetramethylethylenediamine (TEMED)) and then transferred to PVDF membranes. After blocking with 5% BSA for 2 h, the membranes were incubated overnight at 4℃ with AKT, p–AKT, GSK3β, p–GSK3β and cleaved caspase 3 antibody. Then the membranes were incubated at room temperature for 2 h in buffer containing anti-rabbit IgG. For the densitometry analysis, images were detected with Image J software.

Behavioral despair tests in mice

Open field test: The locomotion activities were evaluated by recording the total distance and rearing number using a video-tracking system (Shanghai Mobile Datum Information Technology Co., Ltd.), which was performed 30 min after

injection of each compound. Each animal was measured for 5 min.

Tail suspension test: After injection of each compound for 30 min, the mice were fixed on a Tail Suspension Monitor at a distance of 2 cm from the tail tip, which was in a suspended state and the head was more than 10 cm from the ground. After 2 min adaption, the immobility time was recorded for 4 min. The criteria of immobility was that the mice stopped struggling and kept vertically suspended.

Forced swimming test: After injection of each compound for 30 min, the mice were placed in an organic glass drum filled with water (temperature: 23 ± 2 °C). All mice were allowed to swim freely for 6 min, and the duration of immobility in the last 4 min was recorded. Each mouse was judged to be immobile when it stopped struggling, remained floating motionless in water, and only made those movements necessary to keep its head above water.

Results

The parameters of OPLS–DA analysis

The model parameters (R2Y and Q2) of OPLS-DA analysis were 0.999 and 0.998, respectively. The parameters were both greater than 0.9 and the difference between them was less than 0.3, indicating that the model had good fitting degree and prediction. Permutation test was used to perform external verification on the model by replacing Y classification labels 200 times randomly, and the results showed that the R2 and Q2 were 0.432 and -0.09089, respectively, indicating there was no over–fitting phenotype in the model.

Table S2. Characterization of chemical constituents in *C. desertocola* and *C. tubulosa* aqueous extracts by UPLC–QTOF–MS/MS

No.	t_R(min)	Measured Mass (Da)	Error (mDa)	Formula	MS/MS fragment ions (Da)	Identification	Source
1	0.593	181.0712	0.56	$C_6H_{14}O_6$	101.0242, 146.8687	mannitol*	CDE/CTE
2	1.832	373.1138	0.22	$C_{16}H_{22}O_{10}$	123.0451, 193.0503	geniposidic acid isomer	CDE/CTE
3	2.717	373.1138	0.22	$C_{16}H_{22}O_{10}$	123.0451, 167.0708, 211.0613	geniposidic acid*	CDE/CTE
4	4.487	375.1292	0.47	$C_{16}H_{21}O_{10}$	151.0754, 169.0867, 213.0762	8–epiloganic acid isomer	CDE/CTE
5	5.195	461.1661	0.35	$C_{20}H_{30}O_{12}$	161.0447, 315.1080, 461.1663	decaffeoylverbascoside*	CDE/CTE
6	5.253	345.1188	0.31	$C_{15}H_{22}O_9$	299.1146	6–deoxycatalpol*	CDE/CTE
7	5.311	299.1133	0.33	$C_{14}H_{20}O_7$	119.0498	salidroside*	CDE/CTE
8	5.549	375.1294	0.27	$C_{16}H_{24}O_{10}$	151.0763, 169.0865, 213.0764	8–epiloganic acid*	CDE/CTE
9	5.73	649.1989	-0.36	$C_{27}H_{38}O_{18}$	135.0445, 179.0349, 305.0882, 485.1283	kankanose	CDE/CTE
10	7.083	375.1293	0.37	$C_{16}H_{24}O_{10}$	365.1002	adoxosidic acid	CDE/CTE
11	7.496	331.1395	0.34	$C_{15}H_{24}O_8$	161.0446	gluroside	CDE/CTE
12	8.381	475.1815	0.6	$C_{21}H_{32}O_{12}$	113.0240, 161.0445, 329.0769	cistanoside E	CDE
13	8.617	487.1462	-0.49	$C_{21}H_{28}O_{13}$	179.0352, 251.0559, 305.0665, 323.0769	cistanoside F	CDE/CTE
14	9.148	487.1454	0.31	$C_{21}H_{28}O_{13}$	179.0342, 251.0557, 305.0660, 323.0768	cistanoside F isomer	CDE/CTE
15	9.973	503.1769	0.11	$C_{22}H_{32}O_{13}$	135.0445, 161.0452, 315.1077, 443.1543, 461.1663	cistanoside H	CDE/CTE
16	10.268	801.2454	0.48	$C_{35}H_{46}O_{21}$	179.0352, 325.0934, 621.2053, 691.2107	cistantubuloside C1/C2	CDE/CTE
17	10.386	521.2021	0.74	$C_{26}H_{34}O_{11}$	359.1489	lariciresinol–4–O–β–D–glucopyranoside	CDE

						or isomer	
18	11.688	639.1939	-0.84	$C_{29}H_{36}O_{16}$	621.1802	campneoside II or isomer	CDE/CTE
19	11.979	785.2514	-0.43	$C_{35}H_{46}O_{20}$	161.0240, 179.0346, 461.1655, 477.1613, 623.2189	echinacoside*	CDE/CTE
20	12.451	521.2023	0.54	$C_{26}H_{34}O_{11}$	329.1389, 359.1390	lariciresinol–4–O–β–D–glucopyranoside or isomer	CDE
21	12.573	639.1943	-1.24	$C_{29}H_{36}O_{16}$	113.0242, 161.0248, 251.0560, 305.0663, 323.0771, 529.1562, 621.1828	campneoside II*	CDE/CTE
22	13.041	769.2560	0.05	$C_{35}H_{46}O_{19}$	145.0291, 457.1524, 477.1619, 605.2098, 623.2187	poliumoside*	CDE/CTE
23	13.222	785.2504	0.57	$C_{35}H_{46}O_{20}$	161.0239, 477.1613, 623.2190	echinacoside isomer	CDE/CTE
24	13.277	799.2660	0.62	$C_{36}H_{48}O_{20}$	161.0240, 475.1804, 491.1756, 623.2186, 637.2336	cistanoside A*	CDE/CTE
25	13.336	345.1553	0.19	$C_{29}H_{34}O_{15}$	153.0915, 165.0912, 183.1010	kankanoside A or isomer	CDE/CTE
26	13.513	345.1553	0.19	$C_{16}H_{26}O_{8}$	153.0915, 165.0912, 183.1010	kankanoside A or isomer	CDE/CTE
27	13.749	347.1708	0.34	$C_{16}H_{28}O_{8}$	167.1072	kankanoside E or N or isomer	CDE/CTE
28	14.103	623.1983	-0.16	$C_{29}H_{36}O_{15}$	161.0256, 179.0348, 315.1083, 461.1663	verbascoside*	CDE/CTE
29	14.457	799.2663	0.32	$C_{36}H_{48}O_{20}$	161.0242, 637.2353	cistanoside A isomer	CDE
30	14.516	347.1715	-0.36	$C_{16}H_{28}O_{8}$	161.0472, 303.1804	kankanoside E or N or isomer	CDE/CTE
31	14.575	813.2818	0.47	$C_{37}H_{50}O_{20}$	175.0403, 473.1661, 637.2346	cistanoside B	CDE
32	14.87	623.1979	0.24	$C_{29}H_{36}O_{15}$	161.0251, 179.0350, 315.1043, 461.1618	Isoverbascoside*	CDE/CTE

33	14.988	769.2552	0.85	$C_{35}H_{46}O_{19}$	161.0240, 607.2226	cistantubuloside A	CDE/CTE
34	15.106	579.2079	0.41	$C_{28}H_{36}O_{13}$	181.0506, 417.1540	(+)–syringaresinol–O–β–D–glucopyranoside	CDE/CTE
35	15.401	607.2033	-0.07	$C_{29}H_{36}O_{14}$	161.0244, 445.1716	syringalide–A–3’ –α–L–rhamnopyranoside	CDE/CTE
36	15.46	841.2769	0.28	$C_{38}H_{50}O_{21}$	161.0241, 491.1772	cistanoside N or isomer	CDE
37	15.578	637.2144	-0.61	$C_{30}H_{38}O_{15}$	161.0241, 179.0345, 475.1819	cistanoside C	CDE/CTE
38	15.582	753.2615	-0.36	$C_{35}H_{46}O_{18}$	161.0243, 179.0358	kankanoside I	CDE/CTE
39	15.755	607.2033	-0.07	$C_{29}H_{36}O_{14}$	161.0244, 445.1724, 461.1446	isosyringalide–A–3’ –α–L–rhamnopyranoside	CDE/CTE
40	15.873	665.2092	-0.49	$C_{31}H_{38}O_{16}$	161.0255, 315.1088, 461.1666, 503.1775	2’ –acetylverbasocisde*	CDE/CTE
41	15.932	637.2144	-0.61	$C_{30}H_{38}O_{15}$	161.0244, 175.0403, 461.1655, 475.1826	cistanoisde C or isomer	CDE/CTE
42	15.932	591.2088	-0.49	$C_{29}H_{36}O_{13}$	119.0498, 145.0294, 445.1695	osmanthuside B or B6 or isomer	CDE/CTE
43	16.168	621.2184	0.48	$C_{30}H_{38}O_{14}$	145.0293, 461.1634, 475.1826	cistanoside M or isomer	CDE
44	16.227	445.1504	0.01	$C_{23}H_{26}O_{9}$	117.0341, 145.0296, 163.0401	eutigoside A	CDE
45	16.286	665.2087	0.01	$C_{31}H_{38}O_{16}$	161.0242, 315.1078, 461.1672, 503.1761	tubuloside B*	CDE/CTE
46	16.404	649.2141	-0.31	$C_{31}H_{38}O_{15}$	461.1621	salaside D or salaside F or tubuloside E or isomer	CDE
47	16.463	665.2089	-0.19	$C_{30}H_{38}O_{14}$	161.0242, 315.1078, 443.6015, 461.1672, 503.1761, 623.1996	tubuloside B isomer	CDE/CTE
48	16.581	679.2246	-0.24	$C_{32}H_{40}O_{16}$	161.0245, 475.1819, 637.2132	salaside D or cistanoside K or cistansinenside A or isomer	CDE
49	16.64	651.2299	-0.46	$C_{31}H_{40}O_{15}$	475.1833, 505.1740	cistanoside D	CDE
50	16.758	649.2148	0.31	$C_{31}H_{38}O_{15}$	145.0295, 161.0243, 315.1059, 461.1665	salaside D or salaside F or tubuloside E or isomer	CDE
51	16.876	591.2086	-0.29	$C_{29}H_{36}O_{13}$	161.0244	osmanthuside B or B6 or isomer	CDE/CTE

52	17.465	693.2395	0.51	$C_{33}H_{42}O_{16}$	175.0406, 651.2285	cistanoside J or isomer	CDE

CTE: *C. tubulosa* aqueous extracts; CDE: *C. desertocola* aqueous extracts; *: identification by reference standards

Table S3 Validation results of LC–MS/MS method for detecting certain compounds in *C. deserticola* and *C. tubulosa* aqueous extracts

Compound	Linear regression equation	R^2	Linear rang (ng/mL)	LOD (ng/mL)	LOQ (ng/mL)	Precision (RSD %)		Reproducibility (RSD%)	Stability (RSD%)	Recovery (%)
						Intra–day (n=6)	Inter–day (n=6)	(n=6)	(n=6)	
Echinacoside	Y=0.00876X–0.0178	0.9992	100–100000	0.1	0.5	3.12	3.26	2.38	4.22	93.1–103.5
Geniposide acid	Y=0.00332X–0.00062	0.9991	10–500	0.3	1.0	2.79	3.17	4.21	3.38	92.4–102.3
8–Epiloganic acid	Y=0.312X+0.000627	0.9997	1.5–2000	0.4	1.5	1.26	2.22	3.29	2.35	95.2–104.1
Verbascoside	Y=0.00512X–0.00371	0.9994	100–100000	0.5	1.0	2.01	3.25	4.23	3.19	93.9–102.4
Isoverbascoside	Y=0.302X–0.212	0.9993	100–20000	1.0	4.0	1.32	2.73	2.92	4.27	92.2–103.2
2'–Acetylverbsacoside	Y=0.602X–0.1032	0.9995	50–5000	0.5	1.0	2.75	3.21	3.17	4.28	93.4–101.6
Campneoside II	Y=0.272X+0.0027	0.9991	2–2000	0.5	1.5	1.24	2.37	3.30	3.19	92.5–98.3
Tubuloside B	Y=0.0815X–0.00261	0.9999	10–1000	1.0	5.0	2.55	3.18	4.29	3.27	100.4–104.3
Cistanoside A	Y=0.0593X–0.00931	0.9999	10–1000	1.0	3.0	2.64	3.02	3.13	4.02	92.4–101.2

Table S4 Linear regression equation, linear range, LLOQ of the analysts

Analyst	Linear regression equation	R^2	Linear rang (ng/mL)	LLOQ (ng/mL)
Echinacoside	Y=0.127X–0.00127	0.9995	10–2000	10
Geniposide acid	Y=0.202X–0.00283	0.9993	10–2000	10
8–Epiloganic acid	Y=0.427X–0.00315	0.9990	10–2000	10
Verbascoside	Y=0.512X–0.00891	0.9992	10–2000	10
Isoverbascoside	Y=0.0721X–0.0009	0.9991	10–2000	10
2’ –Acetylverbsacoside	Y=0.32X–0.000736	0.9995	2–400	2
Campneoside II	Y=0.483X+0.0291	0.9990	10–2000	10
Tubuloside B	Y=0.019X–0.00461	0.9992	20–4000	20
Cistanoside A	Y=0.00702X–0.0000321	0.9994	20–4000	20
caffeic acid	Y=0.328X+0.139	0.9990	10–2000	10
3,4–dihydroxyphenylpropionic acid	Y=0.152X+0.0173	0.9991	10–2000	10
3–hydroxyphenylpropionic acid	Y=0.651X+1.27	0.9990	10–2000	10
hydroxytyrosol	Y=1.29X+0.028	0.9934	10–2000	10

Table S5 Precision, repeatability and stability of the analysts

Analyst	Intra–day RSD (%, n=6)			Inter–day RSD (%, n=6)			Repeatability	Stability
	Low	Medium	High	Low	Medium	High	RSD (%)	RSD (%)
Echinacoside	3.21	4.28	3.43	4.17	3.21	2.38	8.31	4.98
Geniposide acid	5.28	3.20	2.31	3.91	4.18	2.73	5.49	5.21
8–Epiloganic acid	9.39	4.19	2.32	10.23	5.21	4.35	6.17	6.11
Verbascoside	8.34	3.41	3.91	7.25	4.11	3.74	3.28	4.65
Isoverbascoside	2.37	2.38	3.23	2.48	2.76	1.39	5.99	3.77
2'–Acetylverbsacoside	3.28	2.24	2.32	4.15	3.29	3.15	6.06	6.01
Campneoside II	8.20	4.91	5.39	6.94	5.31	4.23	3.65	5.73
Tubuloside B	2.39	2.32	1.32	2.38	3.19	1.37	4.27	4.46
Cistanoside A	3.24	2.17	3.21	3.39	2.31	3.06	5.31	7.31
caffeic acid	12.33	4.29	5.30	13.91	4.28	3.53	7.05	8.92
3,4–dihydroxyphenyl–propionic acid	13.29	8.21	3.21	14.29	5.97	4.28	5.81	6.81
3–hydroxyphenylpropionic	10.82	4.27	4.26	11.65	6.87	3.95	6.67	8.25

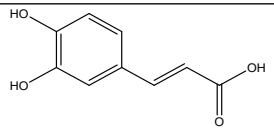
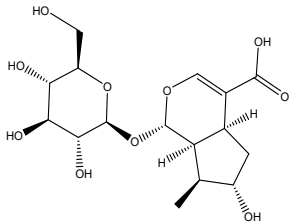
acid								
hydroxytyrosol	9.39	5.36	4.27	8.81	6.81	4.27	4.96	7.10

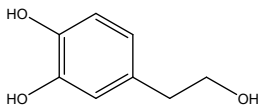
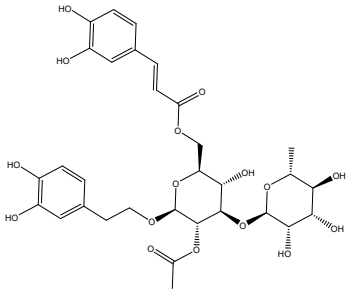
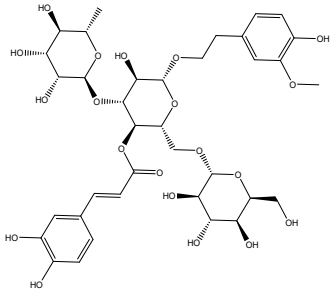
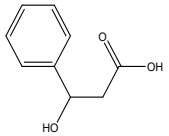
Table S6 Recovery and matrix effects of the analysts

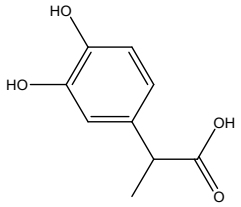
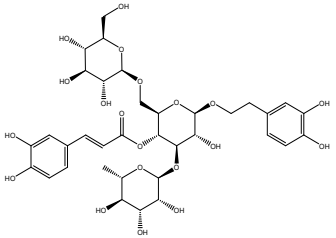
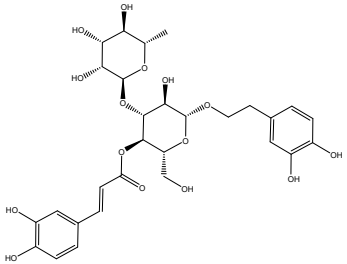
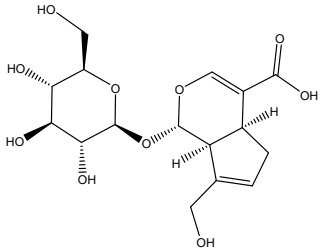
Analyst	Recovery (%, n=3)						Matrix effect
	Low		Medium		High		SSE (%)
	Mean	RSD	Mean	RSD	Mean	RSD	
Echinacoside	105.28	5.09	98.72	2.36	103.01	2.78	84.21
Geniposide acid	98.31	4.26	95.31	3.82	100.26	3.05	92.76
8–Epiloganic acid	87.07	3.42	91.38	4.11	94.99	4.65	110.82
Verbascoside	102.24	6.90	105.10	2.27	102.64	3.53	89.92
Isoverbascoside	88.21	4.36	102.67	3.91	97.31	2.65	90.92
2'–Acetylverbsacoside	96.59	3.77	97.99	2.82	104.28	4.07	100.94
Campneoside II	91.86	3.85	94.31	4.60	103.65	2.64	84.15
Tubuloside B	89.17	4.26	92.66	5.28	110.90	3.45	88.27
Cistanoside A	113.62	6.85	104.82	3.63	94.87	2.39	120.01

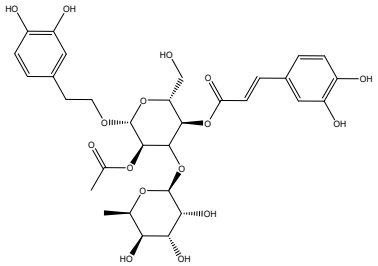
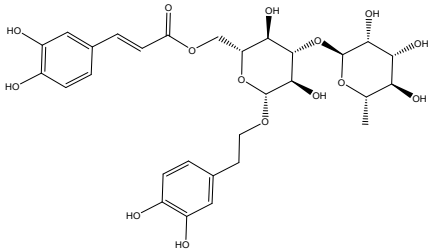
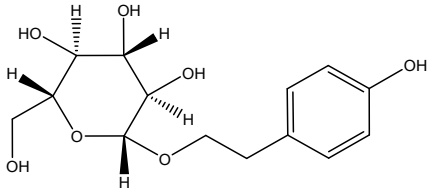
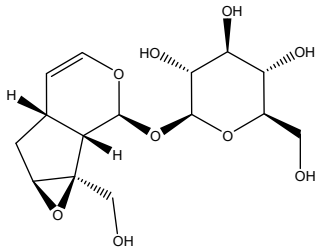
caffeic acid	118.31	5.71	107.01	4.51	103.25	1.80	125.16
3,4–dihydroxyphenyl–propionic acid	105.72	3.05	102.48	3.85	96.92	2.31	104.92
3–hydroxyphenylpropionic acid	119.03	8.46	107.37	4.28	95.29	3.81	104.90
hydroxytyrosol	117.99	10.32	104.6	5.01	92.31	4.28	125.05

Table S7 Information of 15 candidate bioactive compounds of CH

No	Compound	Stucture	Type
1	caffeic acid		Metabolite
2	8–epiloganic acid		prototype (iridoid glycoside)

3	Hydroxytyrosol		metabolite
4	tubuloside B		prototype (phenylethanoid glycoside)
5	cistanoside A		prototype (phenylethanoid glycoside)
6	3–hydroxyphenylpropionic acid		Metabolite

7	3,4–dihydroxyphenylpropionic acid		Metabolite
8	Echinacoside		prototype (phenylethanoid glycoside)
9	Verbascoside		prototype (phenylethanoid glycoside)
10	geniposidic acid		prototype (iridoid glycoside)

11	2’–acetylverbascoside		prototype (phenylethanoid glycoside)
12	Isoverbascoside		prototype (phenylethanoid glycoside)
13	Salidroside		prototype (phenylethanoid glycoside)
14	6–deoxycatalpol		prototype (iridoid glycoside)

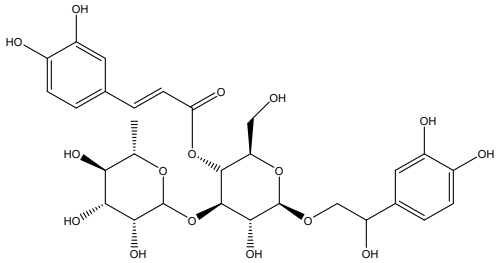
15	campneoside II		prototype (iridoid glycoside)

Table S8 Toxicity test results of each compound on PC12 cells (Mean ± SD, n=6)

Compound	Concentration (μM)	Cell viability (%)	Compound	Concentration (μM)	Cell viability (%)	Compound	Concentration (μM)	Cell viability (%)
Caffeic acid	0	96.7±2.78	3–Hydroxypheylpropionic acid	0	98.5±1.67	Hydroxytyrosol	0	97.3±2.54
	6.25	94.1±1.26		12.5	95.2±2.15		12.5	95.6±1.23
	12.5	95.2±1.90		25	87.3±1.53		25	96.1±2.42
	25	89.5±2.62		50	79.4±2.16		50	87.9±1.26
	50	84.8±3.54		100	70.6±1.54		100	83.6±1.07
3,4–dihydroxypheylpropionic acid	0	97.3±1.42	tubuloside B	0	96.3±2.04	2'–acetylverbascoside	0	98.6±1.26
	12.5	93.3±1.38		12.5	95.8±2.51		12.5	95.2±2.49
	25	92.9±2.17		25	91.3±1.28		25	94.3±1.08
	50	87.6±1.23		50	85.3±1.55		50	86.4±2.54
	100	79.2±3.15		100	76.6±2.38		100	76.2±1.99
verbascoside	0	98.1±2.56	geniposidic acid	0	98.4±1.54	isoverbascoside	0	98.1±1.28
	25	97.0±1.92		25	96.2±2.15		25	96.3±2.17
	50	94.9±2.35		50	93.6±1.03		50	93.2±1.06

	100	85.1±2.67		100	86.2±2.54		100	88.2±1.29
	200	75.2±2.15		200	79.3±1.26		200	79.6±1.05
	0	98.2±1.65		0	98.1±2.35		0	97.3±1.25
	25	96.9±2.16		25	95.6±1.27		25	96.1±2.53
6–deoxycatalpol	50	95.3±2.03	salidroside	50	94.5±1.85	campneoside II	50	93.9±1.26
	100	88.7±1.28		100	86.3±1.33		100	87.2±1.58
	200	80.1±2.54		200	79.1±2.64		200	78.5±2.34
	0	98.2±1.45		0	97.4±2.53		0	96.2±2.51
	25	96.9±2.15		25	96.3±1.40		25	95.6±1.09
8–epiloganic acid	50	93.5±1.27	cistanoside A	50	94.2±2.16	echinacoside	50	93.3±2.65
	100	85.1±2.04		100	86.4±1.65		100	87.1±1.06
	200	75.9±1.32		200	77.6±2.15		200	78.2±1.24

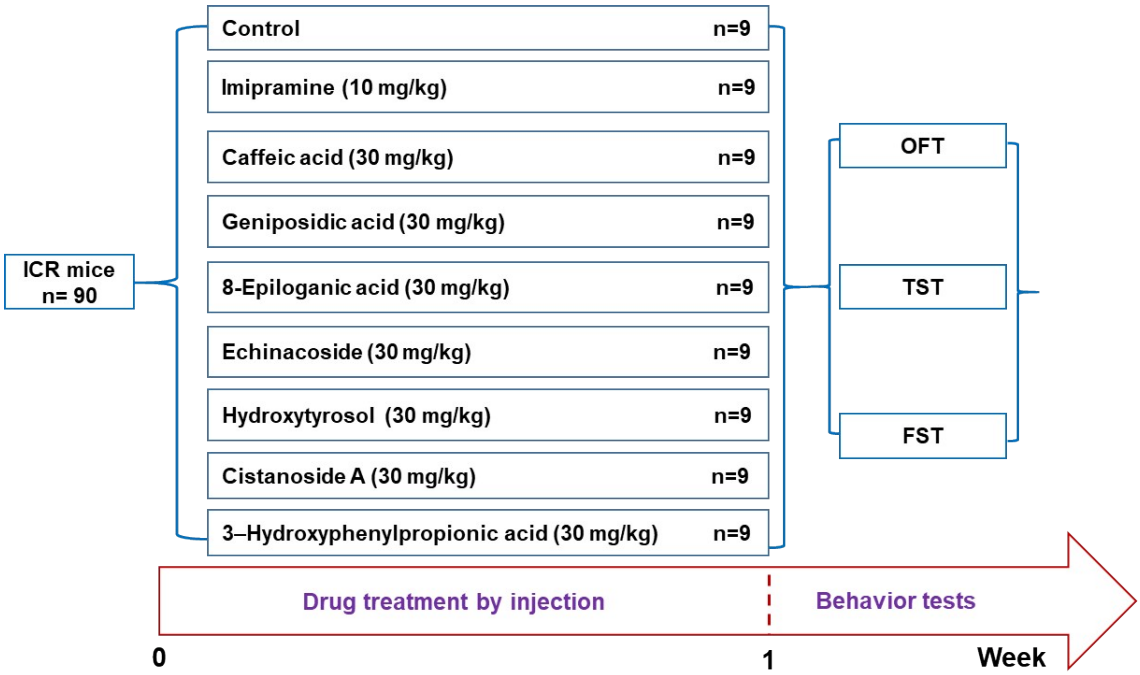


Fig. S1 The flow chart of animal experiments for behavioral despair tests in mice

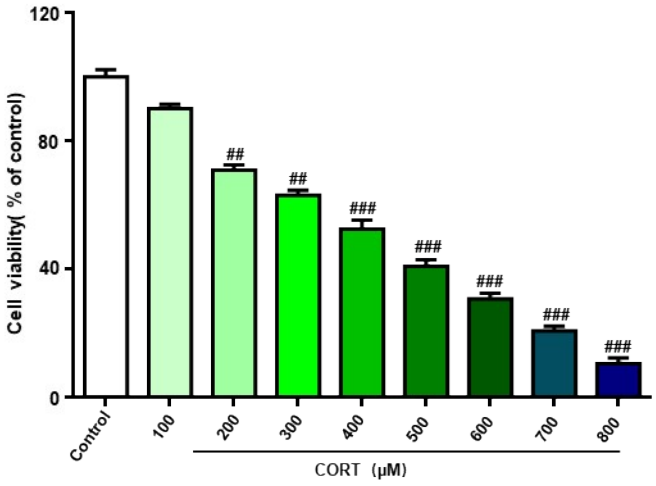


Fig. S2 Cell viability of PC12 cells with co–incubation of corticosterone for 48 h